

OXIME SUBSTITUTED IMIDAZO RING COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/520,418, filed on November 14, 2003, which is incorporated herein in its entirety.

BACKGROUND

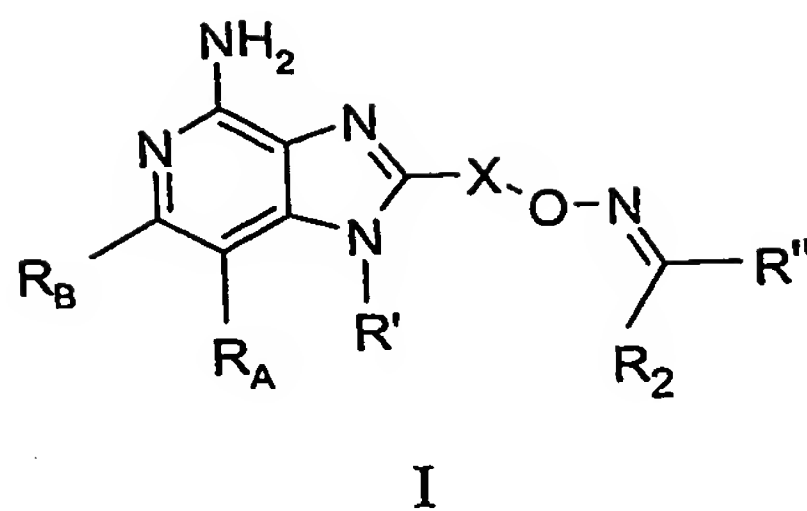
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinoliny)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders.

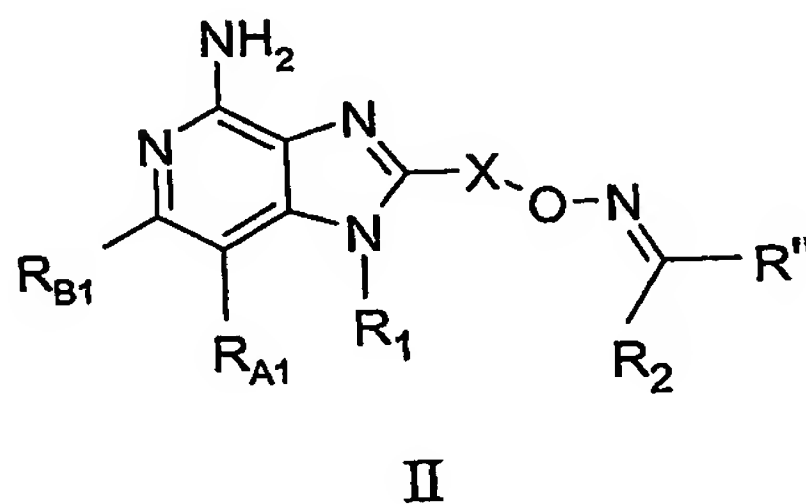
There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula I:



and, more particularly, compounds of the following Formula II:



wherein: R', R'', R_A, R_B, R_{A1}, R_{B1}, R₁, R₂, and X are as defined below.

The compounds of Formulas I and II are useful as immune response modifiers (IRMs) due to their ability to induce cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions, such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal, by administering an effective amount of one or more compounds of Formula I and/or Formula II and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of Formulas I and II and intermediates useful in the synthesis of these compounds.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

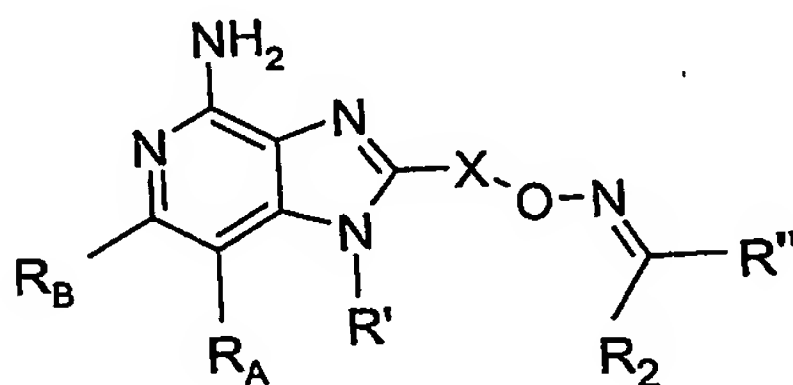
The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

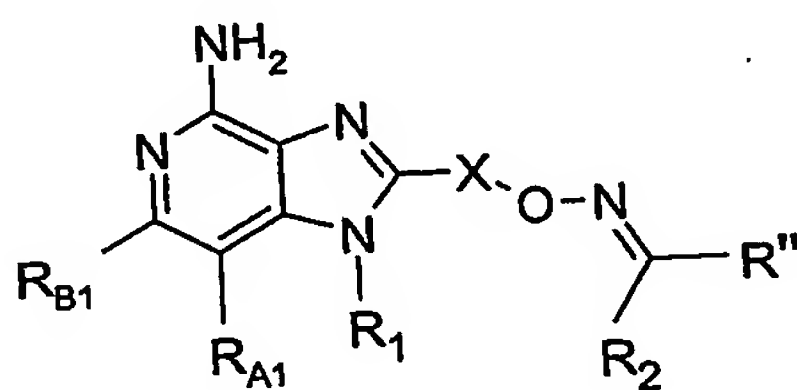
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formulas I through

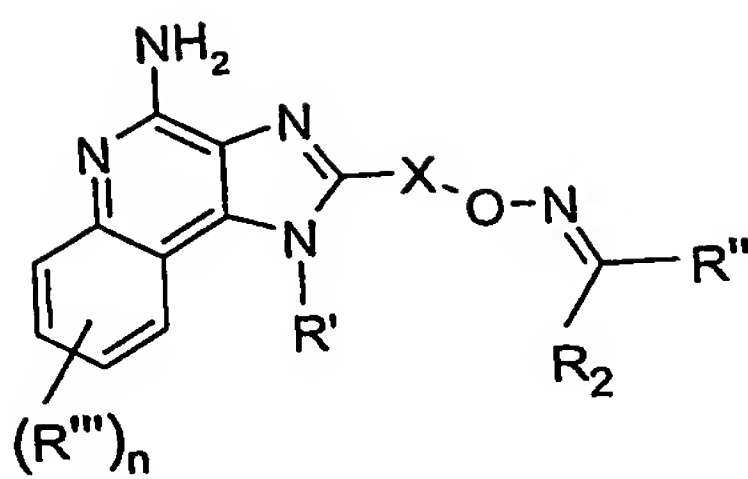
VI:



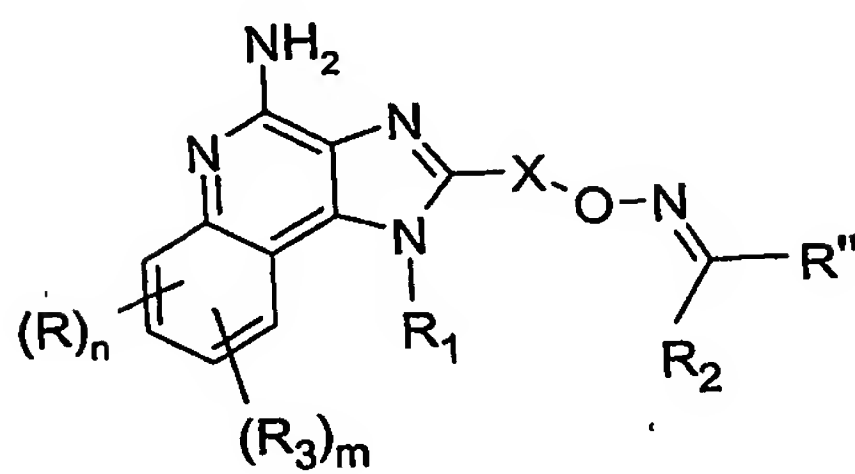
I



II

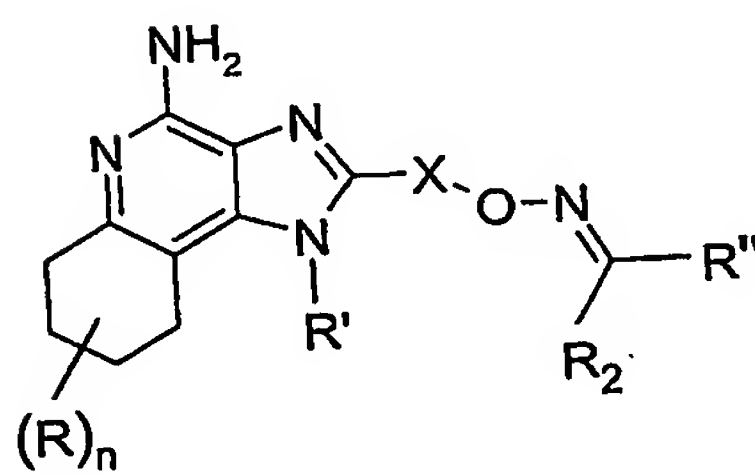


III

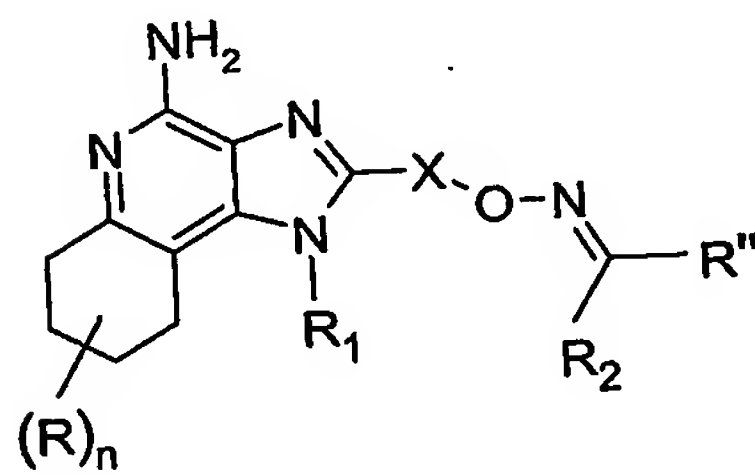


IIIa

5

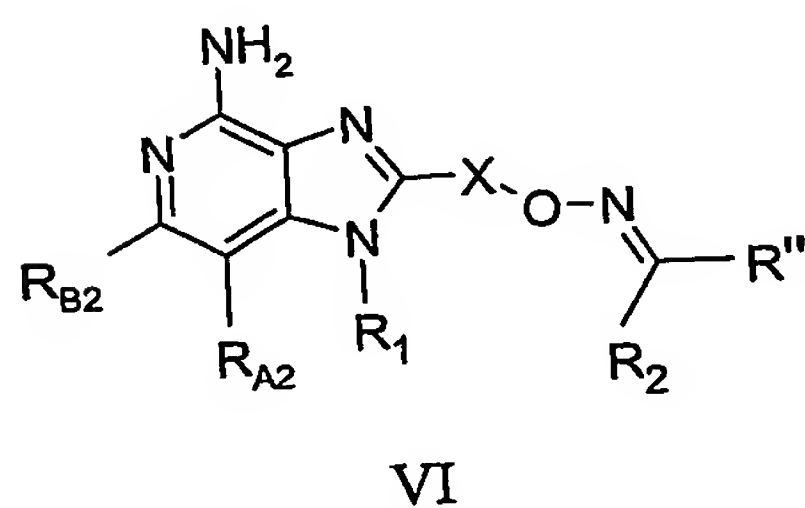
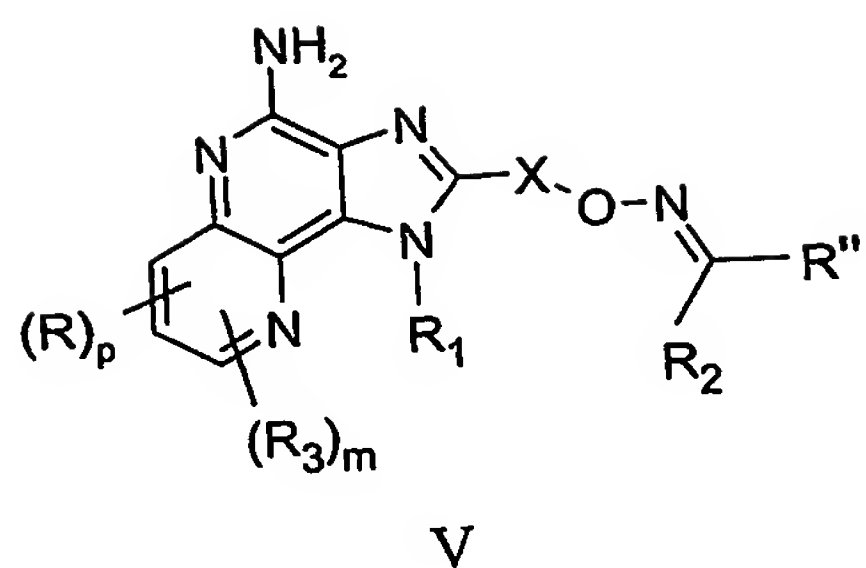


IV



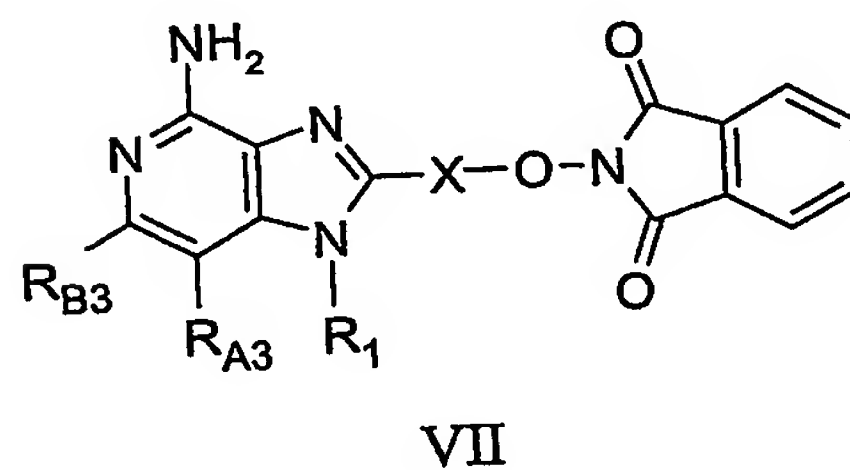
IVa

10

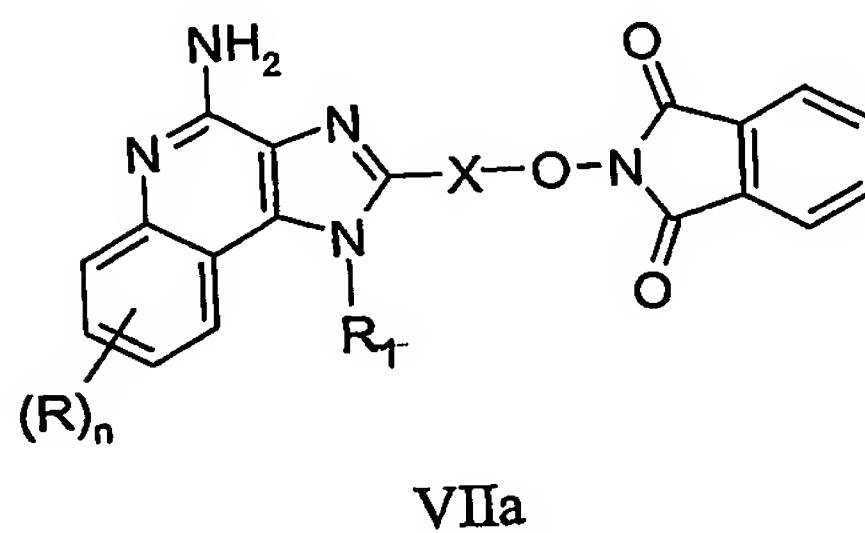


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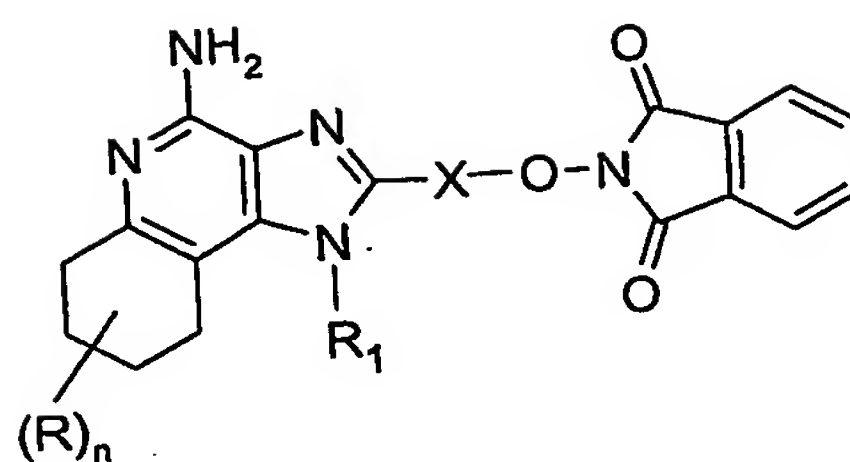
as well as intermediates of the following Formulas VII through VIII (some of which are active compounds):



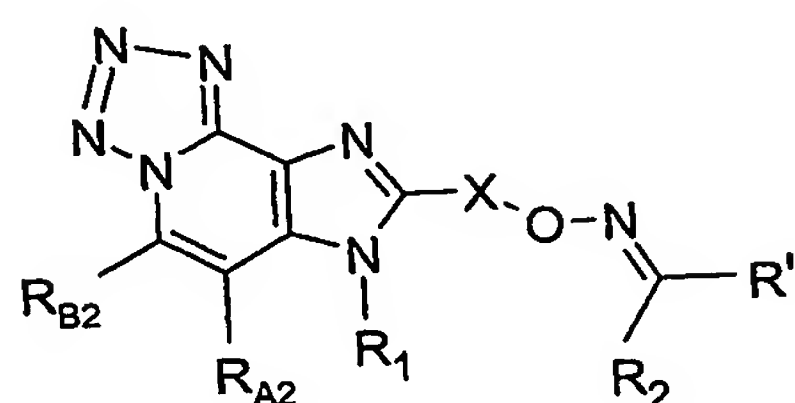
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VIIIb



VIII

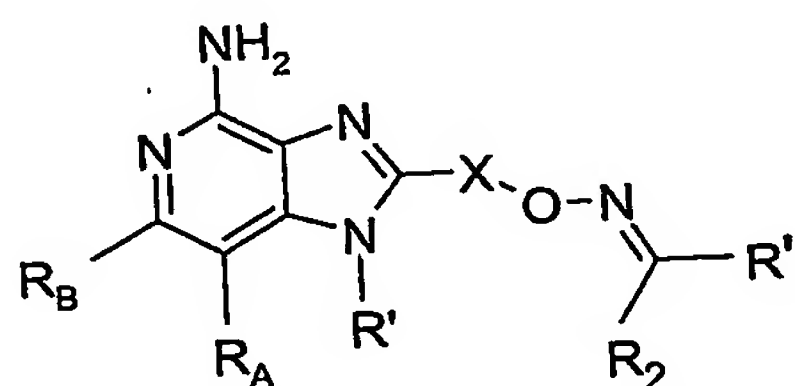
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wherein: R, R', R'', R''', RA, RB, RA1, RB1, RA2, RB2, RA3, RB3, R1, R2, R3, n, m, p, and X are as defined below.

10

In one aspect, the present invention provides compounds of the following Formula

I:



I

15

wherein:

X is C₁₋₁₀ alkylene or C₂₋₁₀ alkenylene;

RA and RB are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

20

alkoxy,
alkylthio, and
-N(R₉)₂;

5 or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

10 R₂ and R'' are independently selected from the group consisting of:

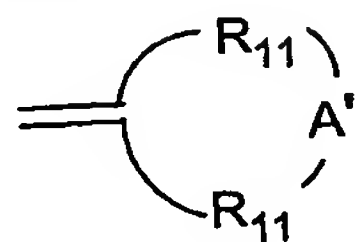
hydrogen,
alkyl,
alkenyl,
aryl,
15 arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

20 alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

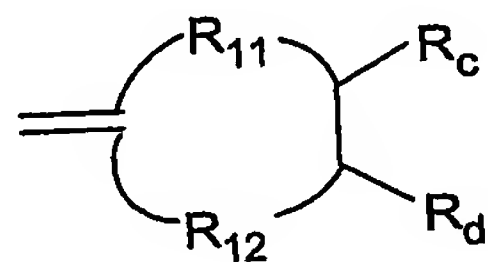
25 hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
amino,
dialkylamino,
30 -S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,

-NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 halogen,
 cyano (i.e., nitrile),
 5 nitro,
 aryl,
 heteroaryl,
 heterocyclyl,
 10 aryloxy,
 arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 -N(R₈)-C(O)-alkyl,
 15 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₂ and R" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

A' is selected from the group consisting of -O-, -S(O)_{0.2}-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

R' is hydrogen or a non-interfering substituent;

R''' is a non-interfering substituent;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₆ is selected from the group consisting of =O and =S;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

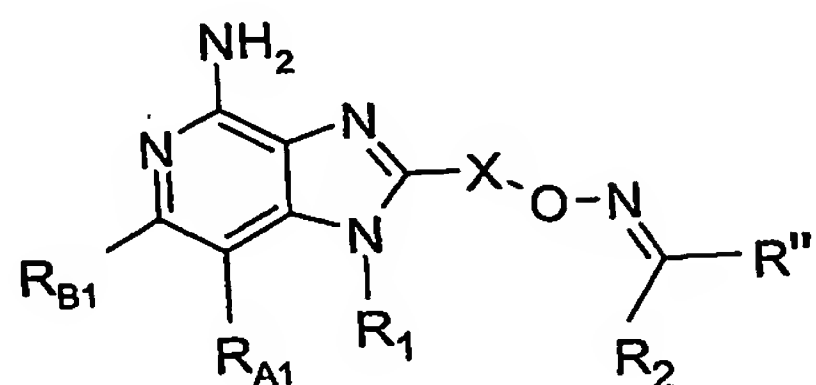
R₁₁ is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₂ is selected from the group consisting of a bond, C₁₋₅ alkylene, and C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom; and

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;
or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

5 II:



II

wherein:

10 X is C₁₋₁₀ alkylene or C₂₋₁₀ alkenylene;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

15

alkenyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring
20 containing one heteroatom selected from the group consisting of N and S, wherein the aryl
or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted
by one R₃ group, or substituted by one R₃ group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated
ring, optionally containing one heteroatom selected from the group consisting of N and S,
25 and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,
 alkenyl,
 haloalkyl,
 alkoxy,
 alkylthio, and
 -N(R₉)₂;

R₁ is selected from the group consisting of:

-R₄,
 -X'-R₄,
 -X'-Y-R₄,
 -X'-Y-X'-Y-R₄,
 -X'-R₅,
 -X''-O-NR_{1a}-Y'-R_{1b}, and
 -X''-O-N=C(R_{1'})(R_{1''});

R₂, R'', R_{1a}, R_{1b}, R_{1'}, and R_{1''} are independently selected from the group consisting

of:

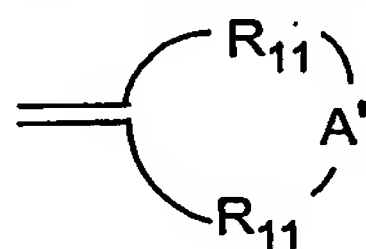
hydrogen,
 alkyl,
 alkenyl,
 aryl,
 arylalkylenyl,
 heteroaryl,
 heteroarylalkylenyl,
 heterocyclyl,
 heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,
 heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected
 from the group consisting of:

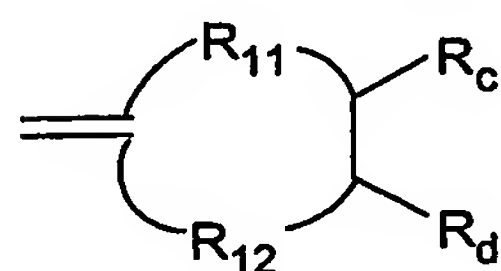
hydroxy,
 alkyl,
 haloalkyl,

hydroxyalkyl,
 alkoxy,
 amino,
 dialkylamino,
 -S(O)₀₋₂-alkyl,
 -S(O)₀₋₂-aryl,
 -NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 halogen,
 cyano,
 nitro,
 aryl,
 heteroaryl,
 heterocyclyl,
 aryloxy,
 arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 -N(R₈)-C(O)-alkyl,
 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₂ and R'' and/or R₁' and R₁'' can join together to form a ring system selected from the group consisting of:

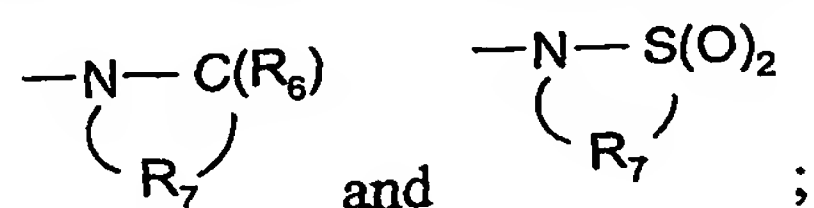


wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

or R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



R_3 is selected from the group consisting of:

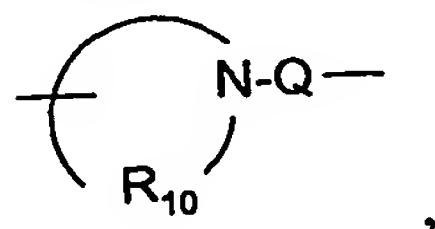
5 $-Z-R_4$,
 $-Z-X'-R_4$,
 $-Z-X'-Y-R_4$,
 $-Z-X'-Y-X'-Y-R_4$, and
 $-Z-X'-R_5$;

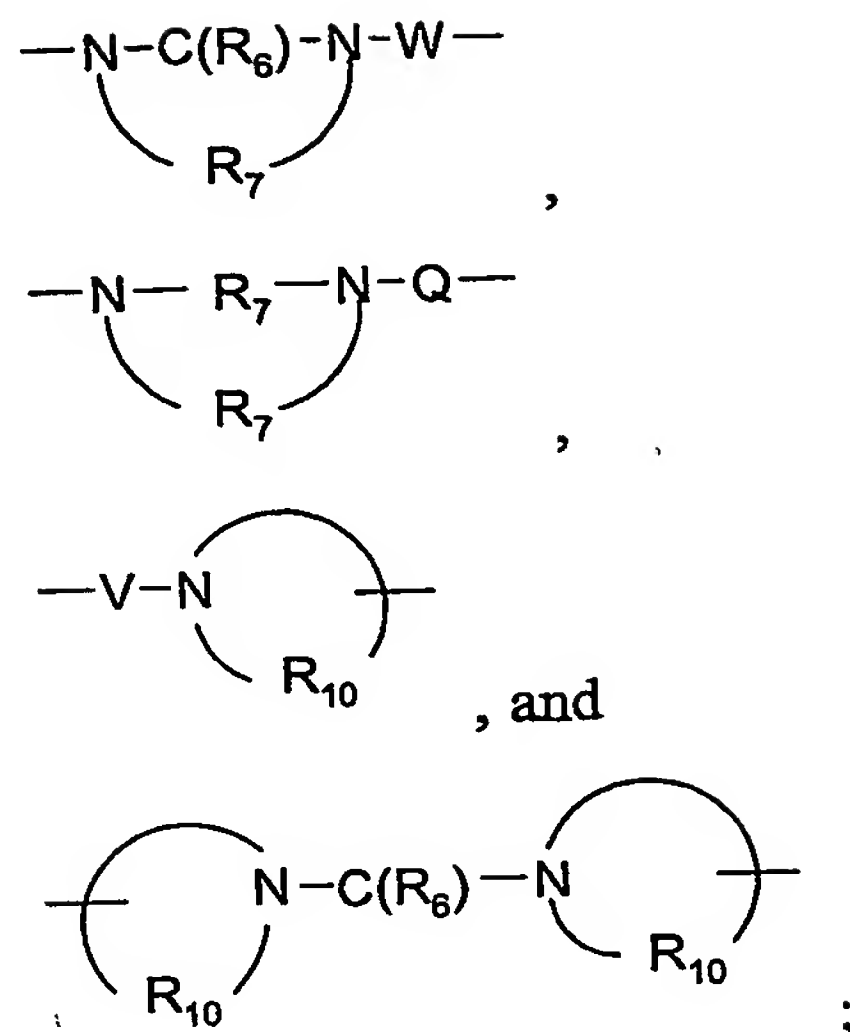
10 X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

15 X" is selected from the group consisting of $-\text{CH}(\text{R}_{13})$ -alkylene- and $-\text{CH}(\text{R}_{13})$ -alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

| | |
|----|--|
| | -S(O) ₀₋₂ -, |
| | -S(O) ₂ -N(R ₈)-, |
| 20 | -C(R ₆)-, |
| | -C(R ₆)-O-, |
| | -O-C(R ₆)-, |
| | -O-C(O)-O-, |
| | -N(R ₈)-Q-, |
| 25 | -C(R ₆)-N(R ₈)-, |
| | -O-C(R ₆)-N(R ₈)-, |
| | -C(R ₆)-N(OR ₉)-, |





5

Y' is selected from the group consisting of:

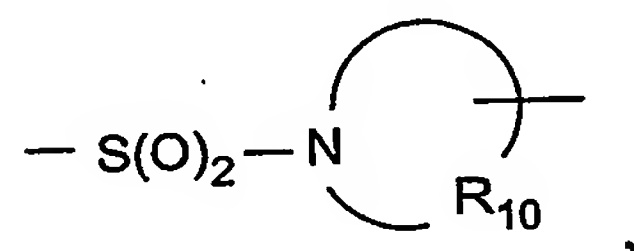
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

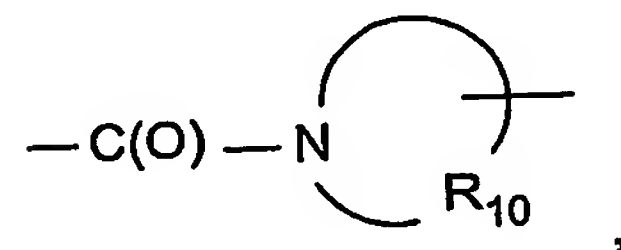
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-S(O)₂-N(R₈)-,

-C(O)-O-,

-C(O)-N(R₈)-,-C(S)-N(R₈)-,

15

-C(O)-N(R₈)-S(O)₂-,-C(O)-N(R₈)-C(O)-,-C(S)-N(R₈)-C(O)-,

-C(O)-C(O)-,

20

-C(O)-C(O)-O-, and

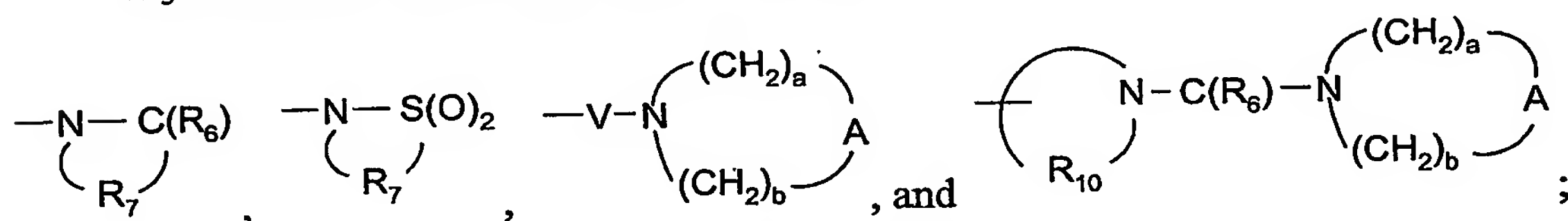
-C(=NH)-N(R₈)-;

Z is a bond or -O-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

5 R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group
10 consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
15 oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of $=O$ and $=S$;

R_7 is C_{2-7} alkylene;

20 R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

25 R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

5 A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

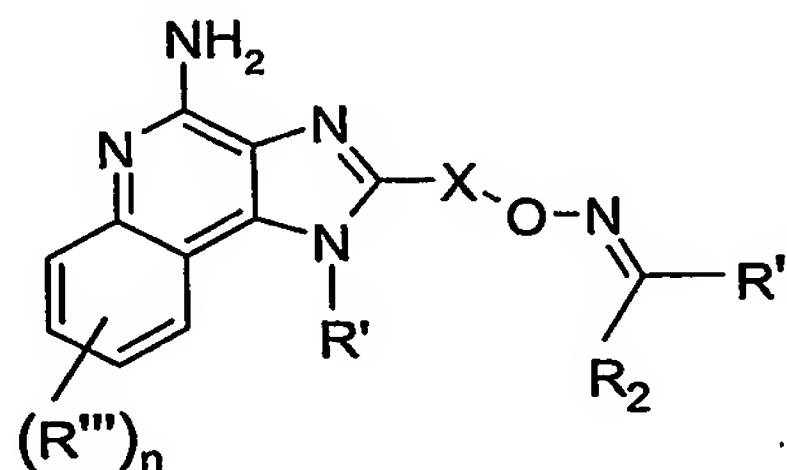
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

10 W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;
or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

15 III:



III

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

20 R_2 and R'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

25 arylalkylenyl,

heteroaryl,

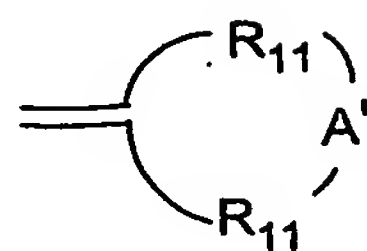
heteroarylalkylenyl,

heterocyclyl,

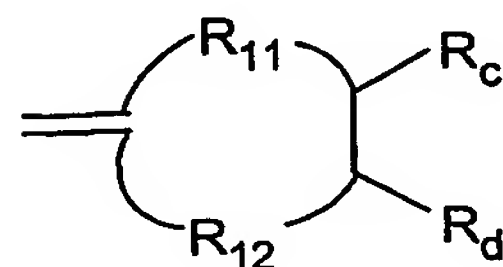
heterocyclalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,
heterocycl, or heterocyclalkylenyl, substituted by one or more substituents selected
from the group consisting of:

5 hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
10 dialkylamino,
-S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,
-NH-S(O)₂-alkyl,
-NH-S(O)₂-aryl,
15 haloalkoxy,
halogen,
cyano,
nitro,
aryl,
20 heteroaryl,
heterocycl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
25 -C(O)-N(R₈)₂,
-N(R₈)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

or R₂ and R" can join together to form a ring system selected from the group
30 consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$,

5 $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing

10 one to four heteroatoms;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_6 is selected from the group consisting of $=O$ and $=S$;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

25 R_9 is selected from the group consisting of hydrogen and alkyl;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

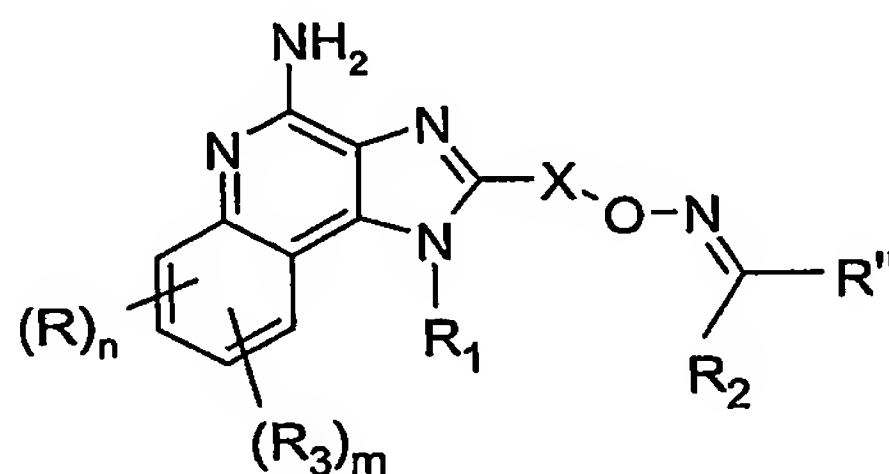
n is an integer from 0 to 4;

R''' is a non-interfering substituent; and

R' is hydrogen or a non-interfering substituent;
or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

IIIa:



IIIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$,

$-X'-Y-X'-Y-R_4$,

-X'-R₅,
 -X''-O-NR_{1a}-Y'-R_{1b}, and
 -X''-O-N=C(R_{1'})(R_{1''});

R₂, R'', R_{1a}, R_{1b}, R_{1'}, and R_{1''} are independently selected from the group consisting

5 of:

hydrogen,
 alkyl,
 alkenyl,
 aryl,
 10 arylalkylenyl,
 heteroaryl,
 heteroarylalkylenyl,
 heterocyclyl,
 heterocyclylalkylenyl, and

15

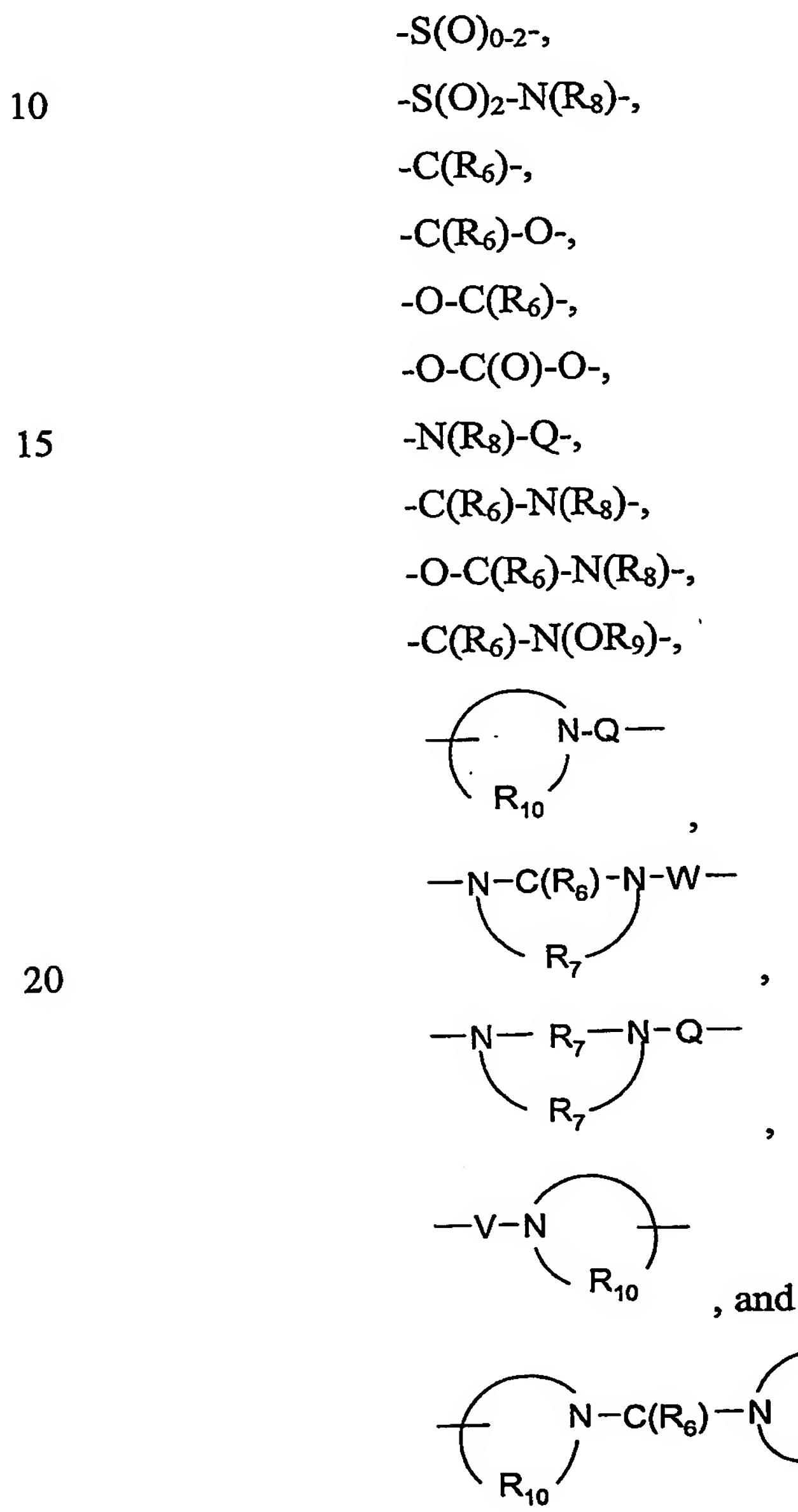
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,
 heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected
 from the group consisting of:

hydroxy,
 alkyl,
 20 haloalkyl,
 hydroxyalkyl,
 alkoxy,
 amino,
 dialkylamino,
 25 -S(O)₀₋₂-alkyl,
 -S(O)₀₋₂-aryl,
 -NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 30 halogen,
 cyano,

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

5 X'' is selected from the group consisting of $-\text{CH}(\text{R}_{13})\text{-alkylene-}$ and $-\text{CH}(\text{R}_{13})\text{-alkenylene-}$, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:



Y' is selected from the group consisting of:

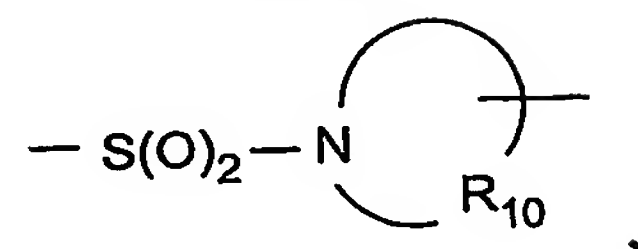
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

-S(O)₂-N(R₈)-,



-C(O)-O-,

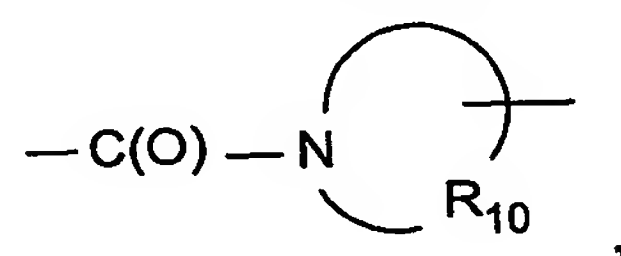
-C(O)-N(R₈)-,

-C(S)-N(R₈)-,

-C(O)-N(R₈)-S(O)₂-,

-C(O)-N(R₈)-C(O)-,

-C(S)-N(R₈)-C(O)-,



-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R₈)-;

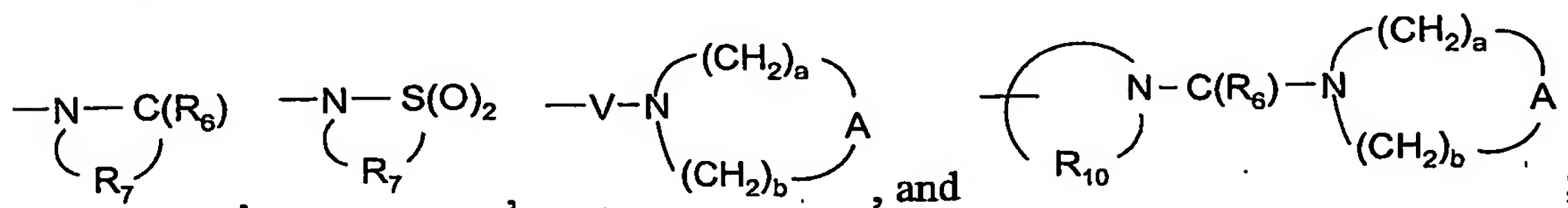
Z is a bond or -O-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy,

mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

5 R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C₂₋₇ alkylene;

10 R_8 is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C₃₋₈ alkylene;

R_{11} is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

15 R_{12} is selected from the group consisting of a bond, C₁₋₅ alkylene, and C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

20 A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

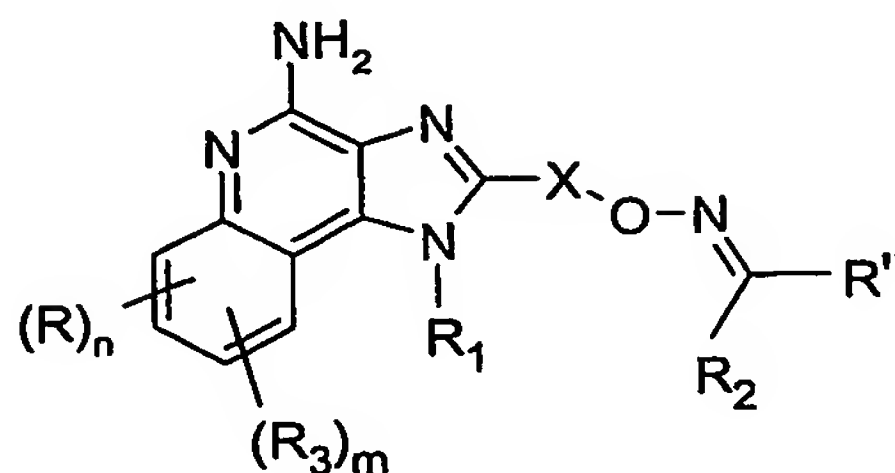
25 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

IIIa:



IIIa

wherein:

X is C₁₋₁₀ alkylene or C₂₋₁₀ alkenylene;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

R₁ is selected from the group consisting of:

-R₄,

-X'-R₄,

-X'-Y-R₄,

-X'-Y-X'-Y-R₄,

-X'-R₅,

-X''-O-NH-Y'-R₁', and

-X''-O-N=C(R₁') (R₁'');

R₂, R'', R₁', and R₁' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

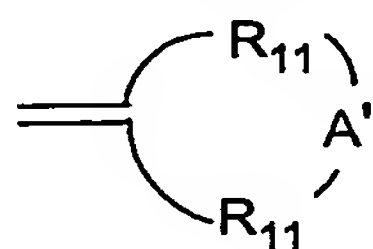
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
5 heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,
heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected
from the group consisting of:

10 hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
15 dialkylamino,
-S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,
-NH-S(O)₂-alkyl,
-NH-S(O)₂-aryl,
20 haloalkoxy,
halogen,
cyano,
nitro,
aryl,
25 heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
30 -C(O)-N(R₈)₂,
-N(R₈)-C(O)-alkyl,

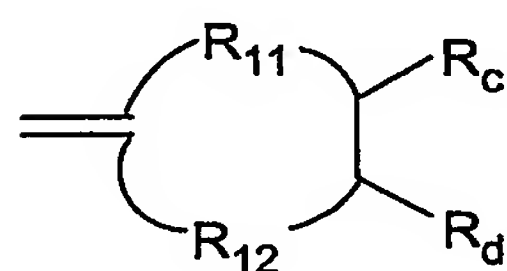
-O-(CO)-alkyl, and

-C(O)-alkyl;

or R_2 and R'' and/or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_3 is selected from the group consisting of:

-Z- R_4 ,

-Z- X' - R_4 ,

-Z- X' -Y- R_4 ,

-Z- X' -Y- X' -Y- R_4 , and

-Z- X' - R_5 ;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X'' is -CH(R_{13})-alkylene- or -CH(R_{13})-alkenylene-;

Y is selected from the group consisting of:

-S(O)₀₋₂-,

-S(O)₂-N(R_8)-,

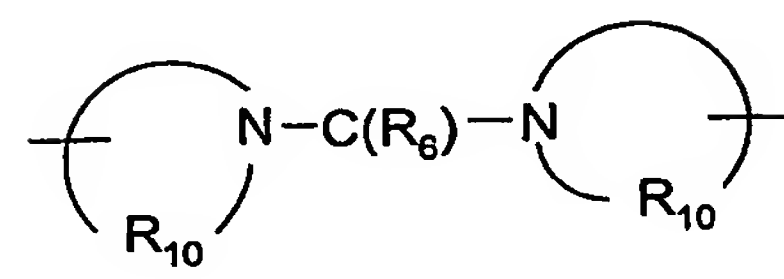
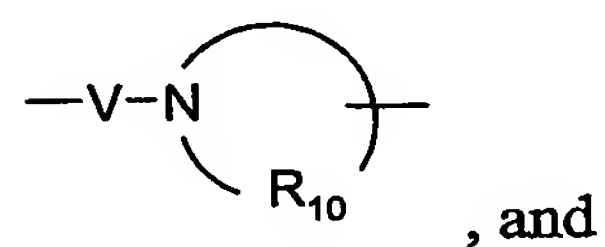
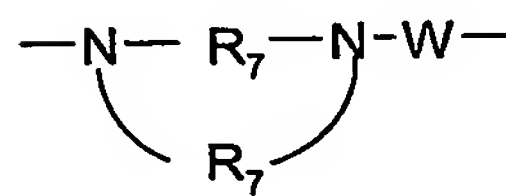
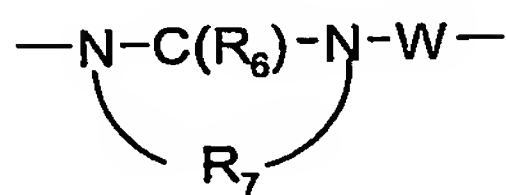
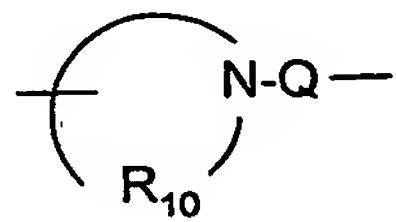
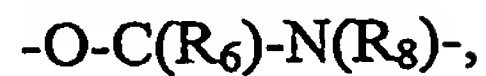
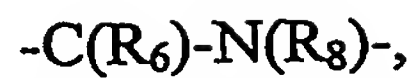
-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

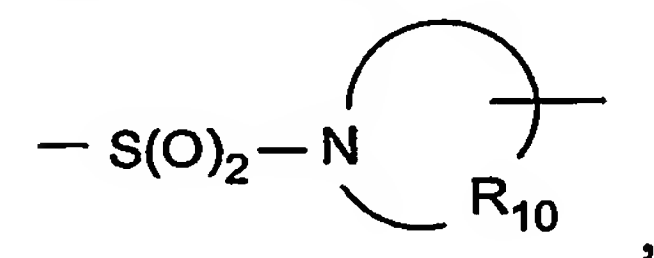
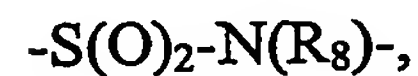
-O-C(O)-O-,

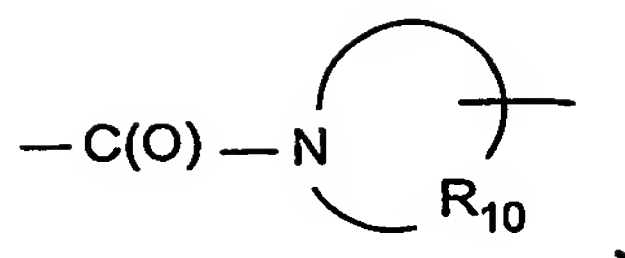
-N(R_8)-Q-,



Y' is selected from the group consisting of:

a bond,





-C(O)-C(O)-,

-C(O)-C(O)-O-, and

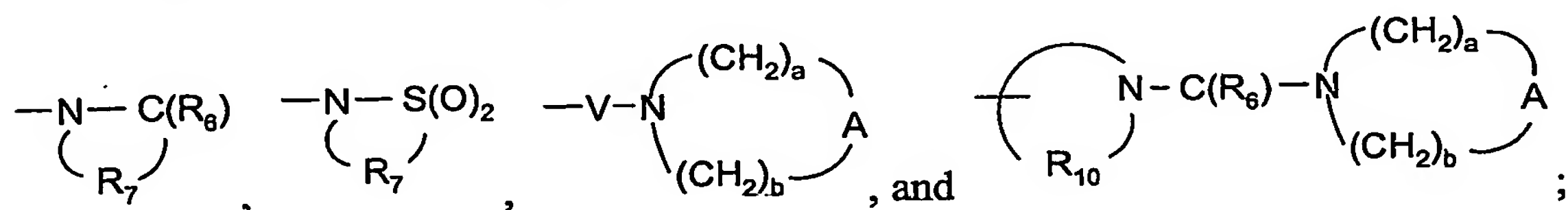
-C(=NH)-N(R₈)-;

5 Z is a bond or -O-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

10 R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group
15 consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
20 oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

25 R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkyl, and aryl-C₁₋₁₀ alkyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

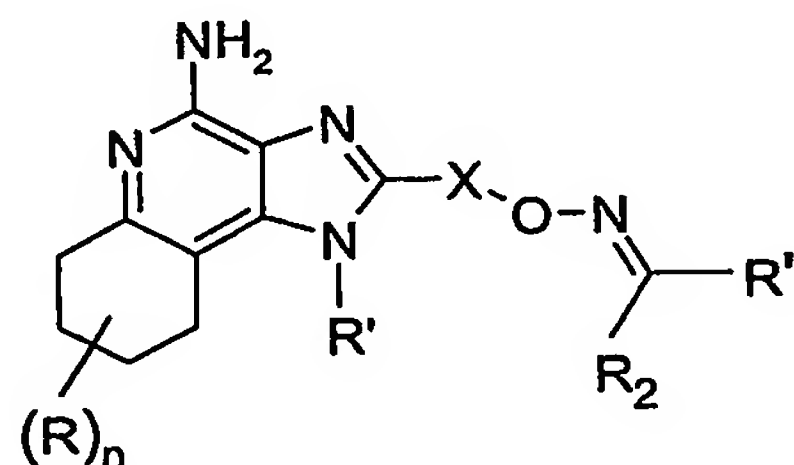
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

IV:



IV

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_2 and R'' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,

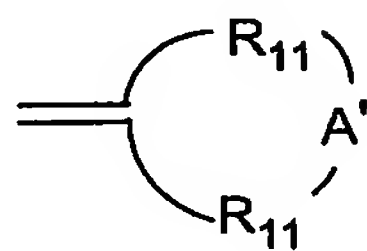
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
5 heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,
heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected
from the group consisting of:

10 hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
15 dialkylamino,
-S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,
-NH-S(O)₂-alkyl,
-NH-S(O)₂-aryl,
20 haloalkoxy,
halogen,
cyano,
nitro,
aryl,
25 heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;
-C(O)-O-alkyl,
30 -C(O)-N(R₈)₂,
-N(R₈)-C(O)-alkyl,

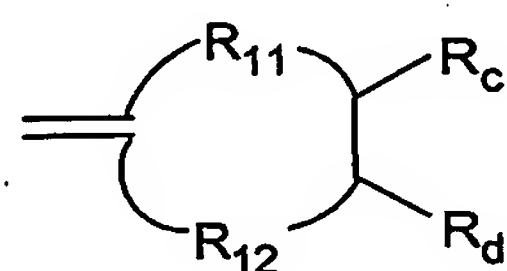
-O-(CO)-alkyl, and

-C(O)-alkyl;

or R₂ and R" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₆ is selected from the group consisting of =O and =S;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl,

C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₁ is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

5 R₁₂ is selected from the group consisting of a bond, C₁₋₅ alkylene, and C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R is selected from the group consisting of:

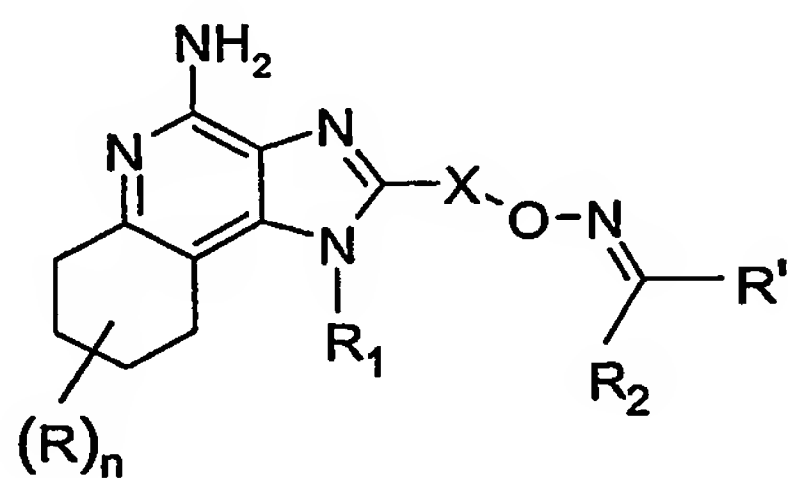
10 halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
15 alkylthio, and
-N(R₉)₂;

n is an integer from 0 to 4; and

R' is hydrogen or a non-interfering substituent;
or a pharmaceutically acceptable salt thereof.

20

In one aspect, the present invention provides compounds of the following Formula IVa:



IVa

25 wherein:

X is C₁₋₁₀ alkylene or C₂₋₁₀ alkenylene;

R is selected from the group consisting of:

halogen,

hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

n is an integer from 0 to 4;

R₁ is selected from the group consisting of:

-R₄,
-X'-R₄,
-X'-Y-R₄,
-X'-Y-X'-Y-R₄,
-X'-R₅,
-X''-O-NR_{1a}-Y'-R_{1b}, and
-X''-O-N=C(R_{1'})(R_{1''});

R₂, R'', R_{1a}, R_{1b}, R_{1'}, and R_{1''} are independently selected from the group consisting

of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

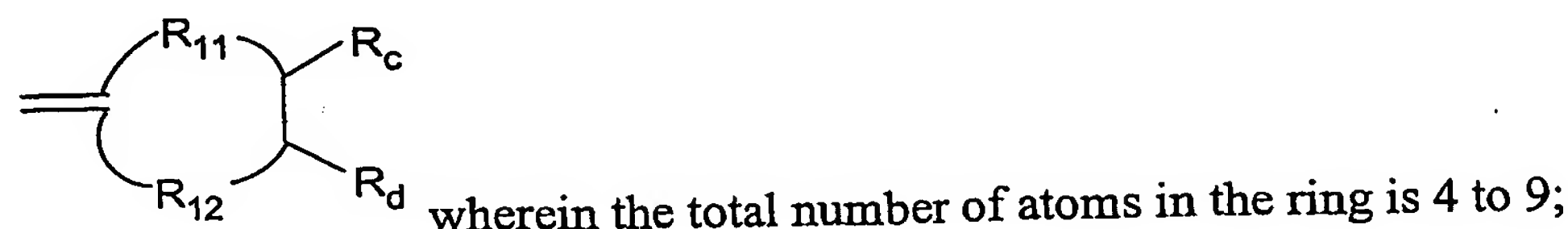
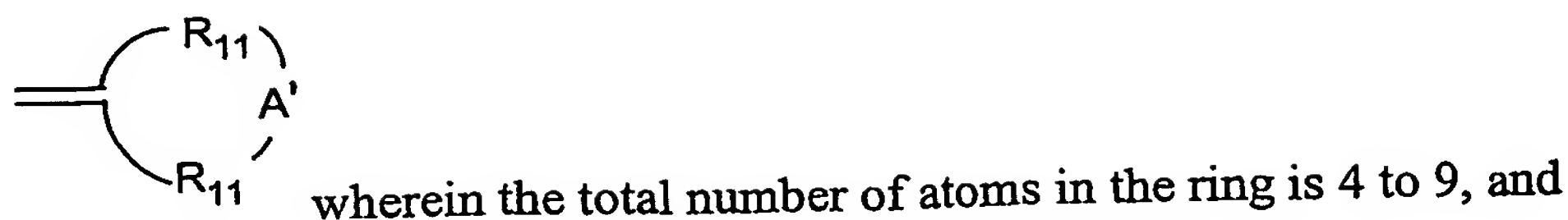
heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected

from the group consisting of:

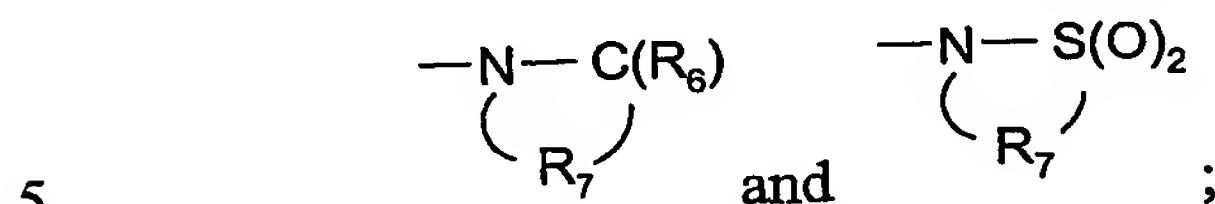
hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
5 amino,
dialkylamino,
-S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,
-NH-S(O)₂-alkyl,
10 -NH-S(O)₂-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
15 aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
20 -C(O)-O-alkyl,
-C(O)-N(R₈)₂,
-N(R₈)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

25 or R₂ and R" and/or R₁' and R₁" can join together to form a ring system selected from the group consisting of:



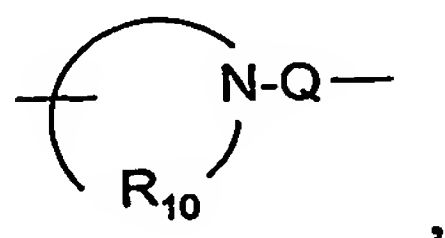
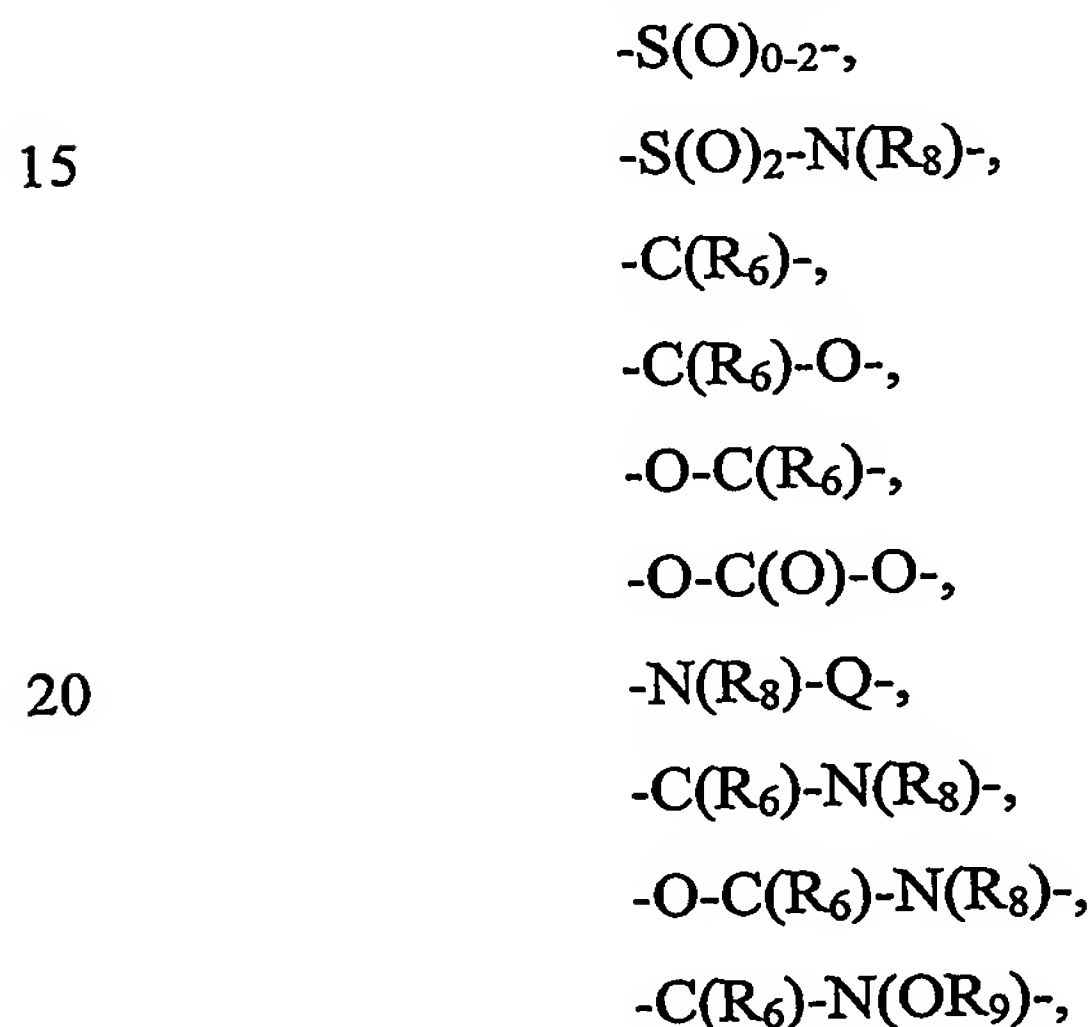
or R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

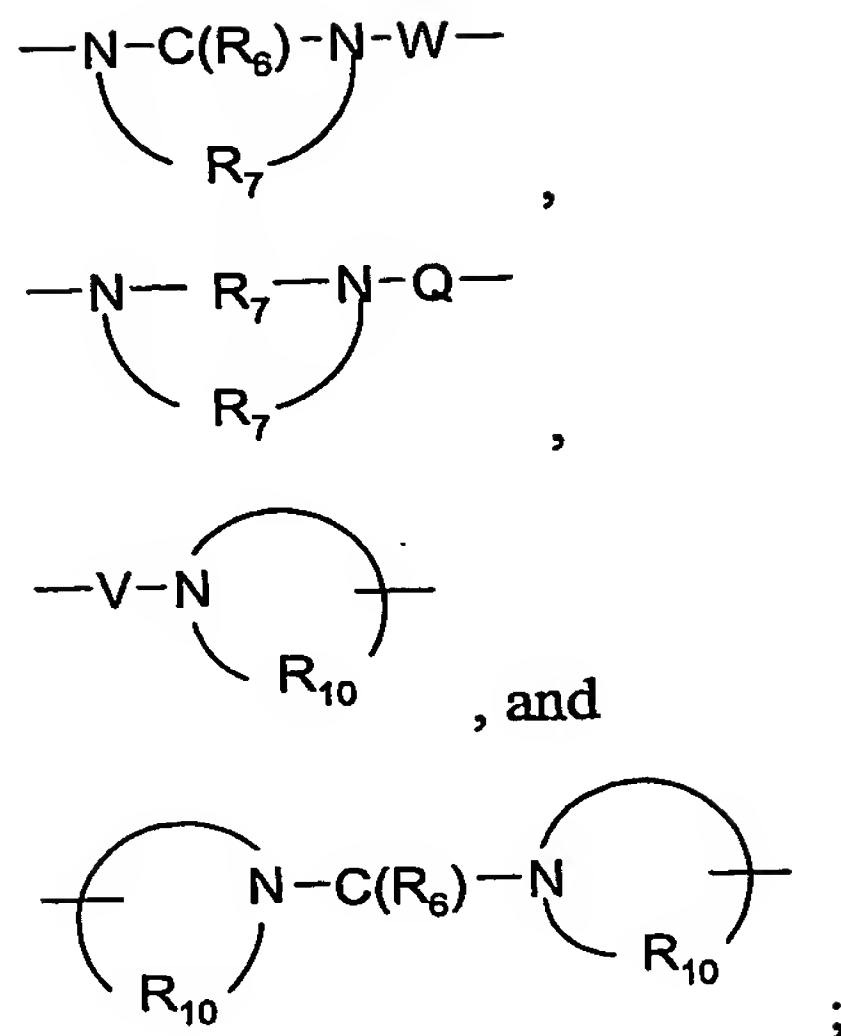


X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

10 X'' is selected from the group consisting of -CH(R₁₃)-alkylene- and -CH(R₁₃)-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:





5

Y' is selected from the group consisting of:

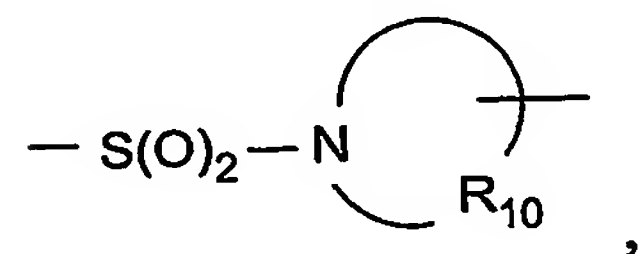
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,-S(O)₂-N(R₈)-,

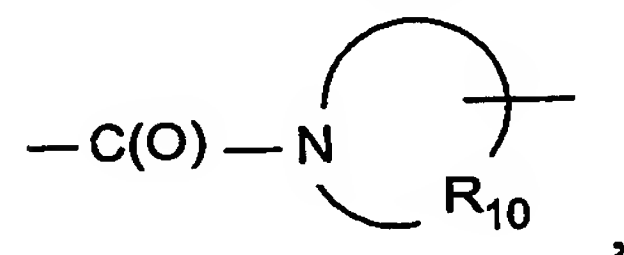
10



-C(O)-O-,

-C(O)-N(R₈)-,-C(S)-N(R₈)-,-C(O)-N(R₈)-S(O)₂-,-C(O)-N(R₈)-C(O)-,-C(S)-N(R₈)-C(O)-,

15



-C(O)-C(O)-,

-C(O)-C(O)-O-, and

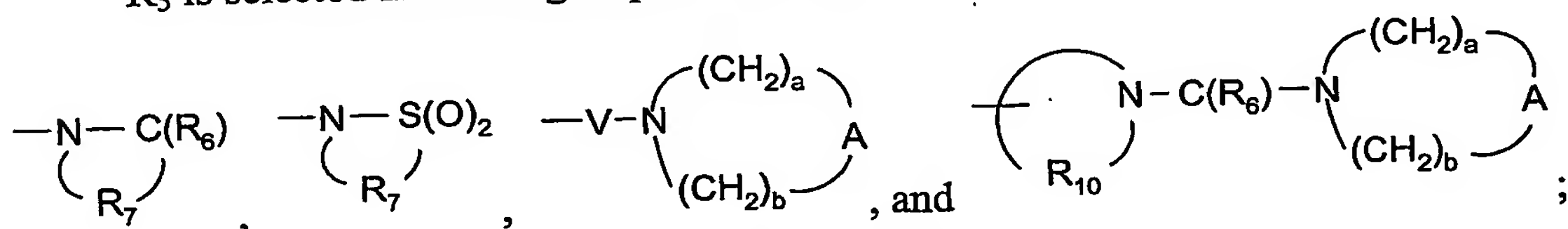
-C(=NH)-N(R₈)-;

20

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

5 R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group
10 consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of $=O$ and $=S$;

R_7 is C_{2-7} alkylene;

20 R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

25 R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-\text{CH}_2-$, -O-, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_{0-2}-$, and $-\text{N}(\text{R}_4)-$;

5 A' is selected from the group consisting of -O-, $-\text{S}(\text{O})_{0-2}-$, $-\text{N}(-\text{Q}-\text{R}_4)-$, and $-\text{CH}_2-$;

Q is selected from the group consisting of a bond, $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)-\text{C}(\text{R}_6)-$, $-\text{S}(\text{O})_2-$, $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-\text{W}-$, $-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)-\text{O}-$, and $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$;

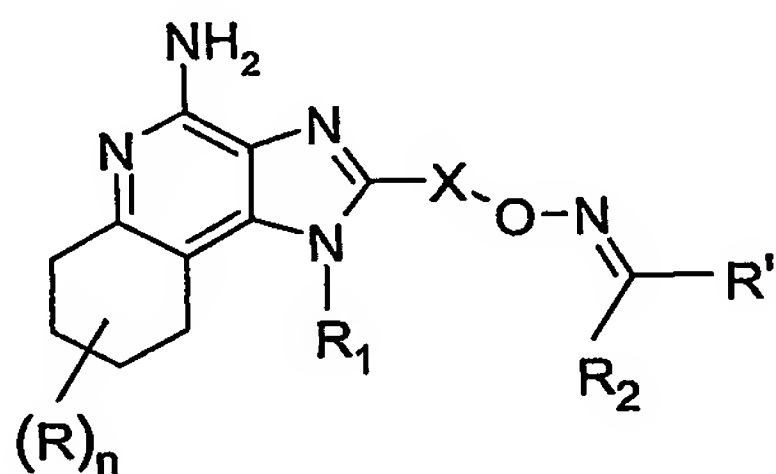
V is selected from the group consisting of $-\text{C}(\text{R}_6)-$, $-\text{O}-\text{C}(\text{R}_6)-$, $-\text{N}(\text{R}_8)-\text{C}(\text{R}_6)-$, and $-\text{S}(\text{O})_2-$;

10 W is selected from the group consisting of a bond, $-\text{C}(\text{O})-$, and $-\text{S}(\text{O})_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

15 IVa:



IVa

wherein:

20 X is C_{1-10} alkylene or C_{2-10} alkenylene;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

25 alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

n is an integer from 0 to 4;

R₁ is selected from the group consisting of:

-R₄,

-X'-R₄,

-X'-Y-R₄,

-X'-Y-X'-Y-R₄,

-X'-R₅,

-X''-O-NH-Y'-R₁', and

-X''-O-N=C(R₁') (R₁'');

R₂, R'', R₁', and R₁'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

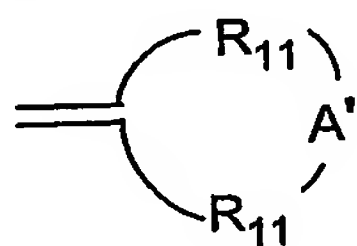
dialkylamino,

-S(O)₀₋₂-alkyl,

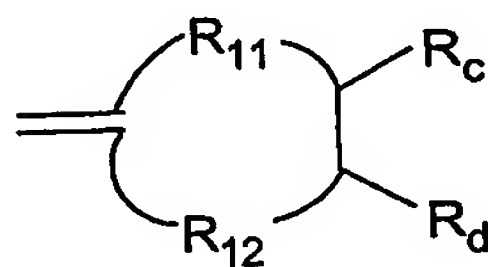
-S(O)₀₋₂-aryl,

-NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 halogen,
 cyano,
 nitro,
 aryl,
 heteroaryl,
 heterocyclyl,
 aryloxy,
 arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 -N(R₈)-C(O)-alkyl,
 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₂ and R" and/or R₁' and R₁" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

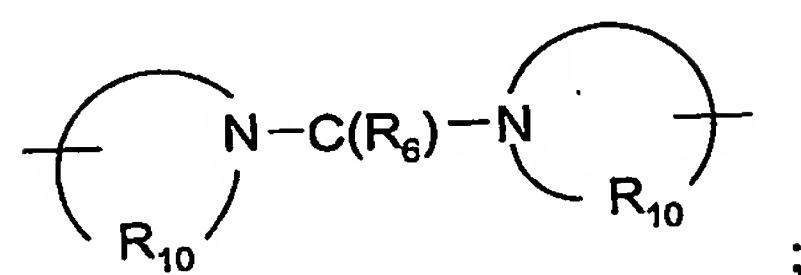
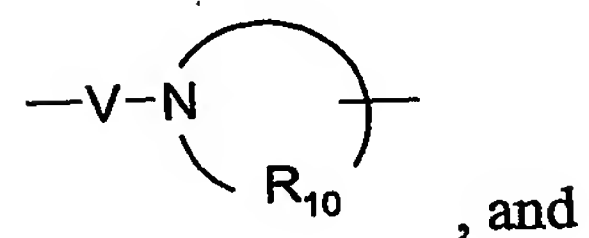
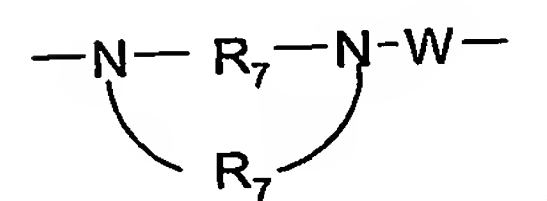
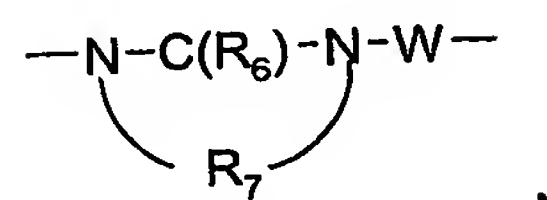
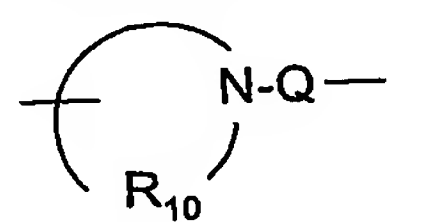
X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is -CH(R₁₃)-alkylene- or -CH(R₁₃)-alkenylene-;

Y is selected from the group consisting of:

-S(O)₀₋₂-

$-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-$,
 $-\text{C}(\text{R}_6)-$,
 $-\text{C}(\text{R}_6)-\text{O}-$,
 $-\text{O}-\text{C}(\text{R}_6)-$,
 $-\text{O}-\text{C}(\text{O})-\text{O}-$,
 $-\text{N}(\text{R}_8)-\text{Q}-$,
 $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$,
 $-\text{O}-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$,
 $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$,



Y' is selected from the group consisting of:

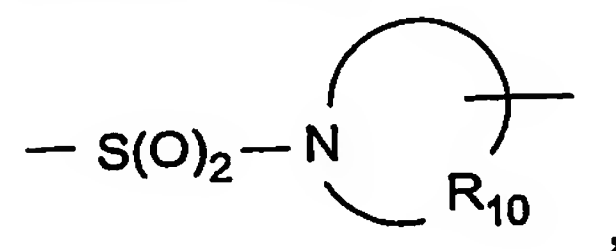
a bond,

$-\text{C}(\text{O})-$,

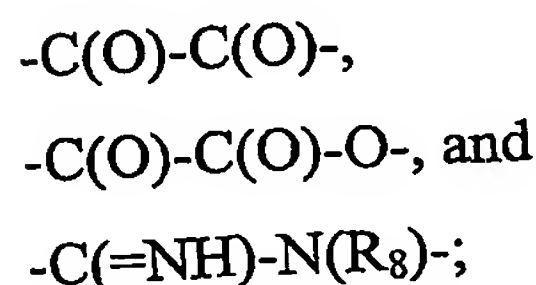
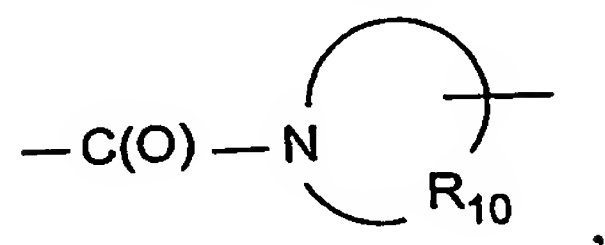
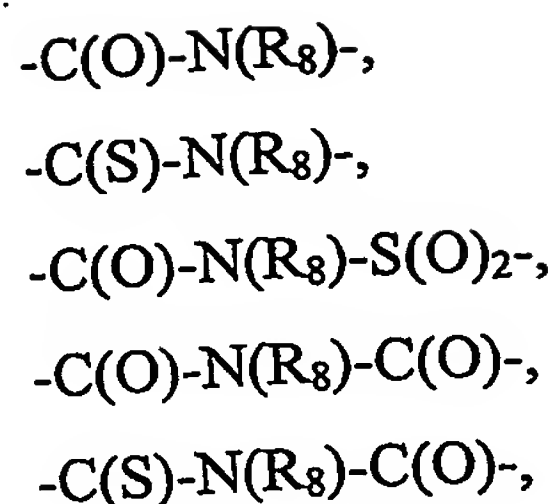
$-\text{C}(\text{S})-$,

$-\text{S}(\text{O})_2-$,

$-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-$,



$-\text{C}(\text{O})-\text{O}-$,

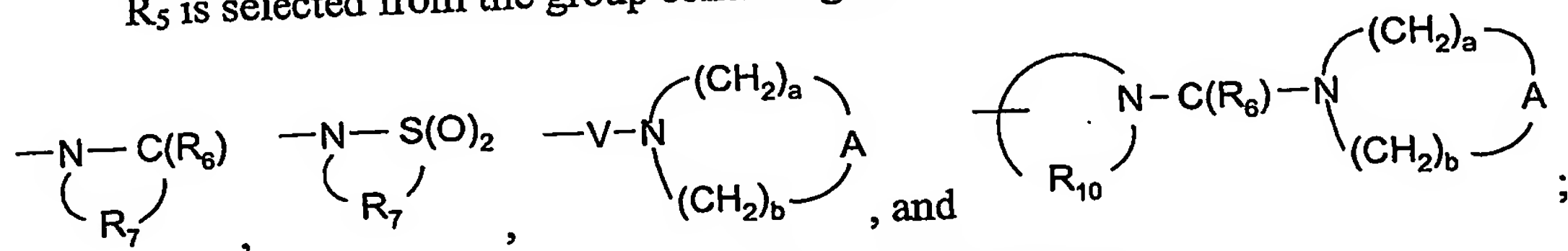


10 R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-\text{N}(\text{R}_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

15 R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group

20 consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

25 R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of $=\text{O}$ and $=\text{S}$;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

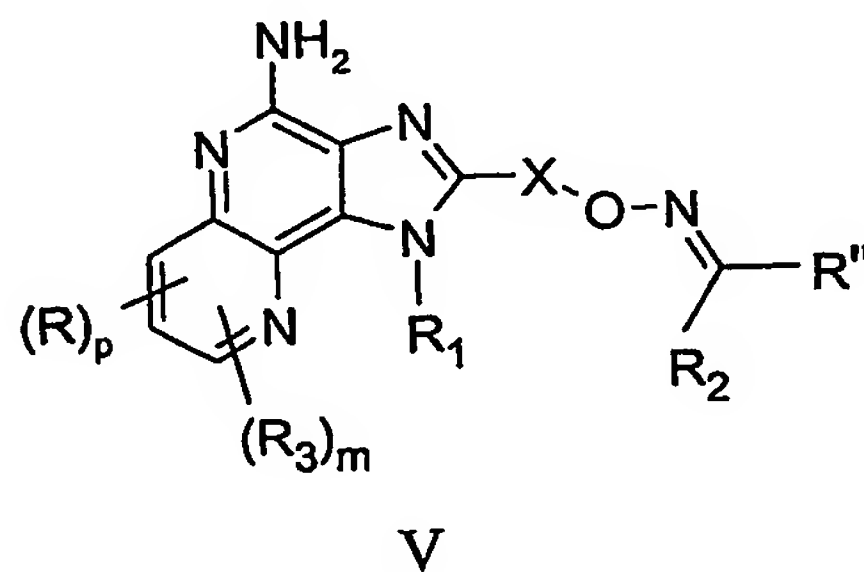
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

V:



wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

R₁ is selected from the group consisting of:

-R₄,
-X'-R₄,
-X'-Y-R₄,
-X'-Y-X'-Y-R₄,
-X'-R₅,
-X''-O-NR_{1a}-Y'-R_{1b}, and
-X''-O-N=C(R_{1'})(R_{1''});

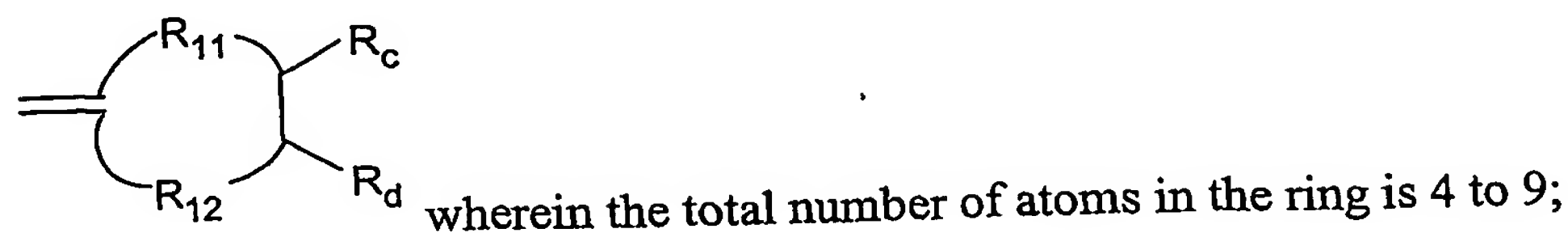
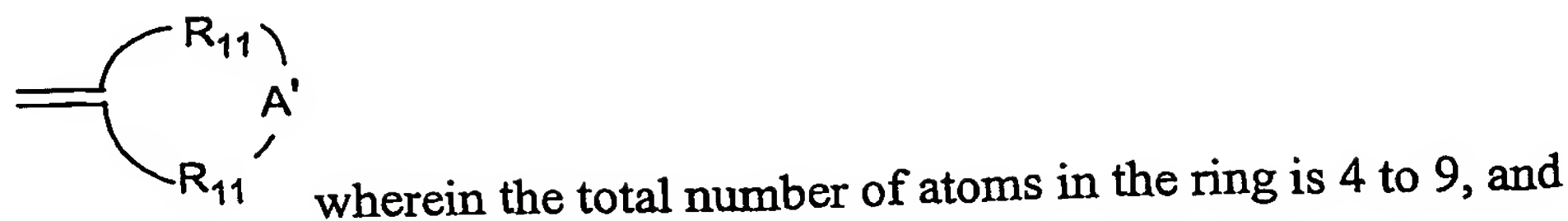
R₂, R'', R_{1a}, R_{1b}, R_{1'}, and R_{1''} are independently selected from the group consisting

of:

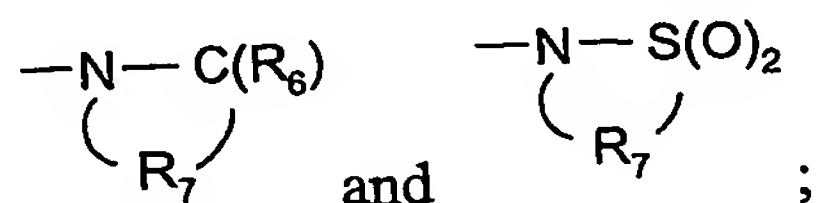
hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,
heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected
from the group consisting of:

5 hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
amino,
dialkylamino,
-S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,
10 -NH-S(O)₂-alkyl,
-NH-S(O)₂-aryl,
haloalkoxy,
halogen,
cyano,
15 nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
20 arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R₈)₂,
-N(R₈)-C(O)-alkyl,
-O-(CO)-alkyl, and
25 -C(O)-alkyl;

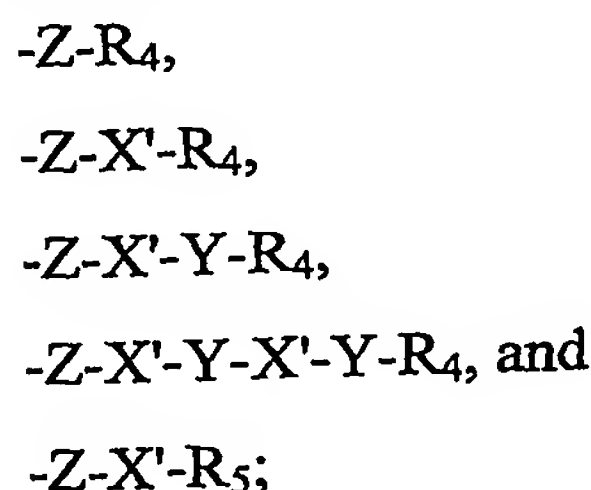
or R₂ and R" and/or R₁' and R₁" can join together to form a ring system selected from the group consisting of:



or R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



R_3 is selected from the group consisting of:



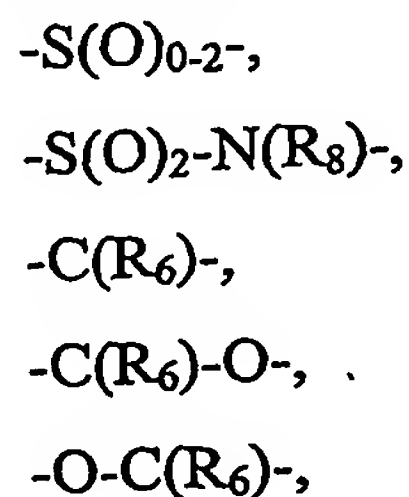
p is an integer from 0 to 3;

m is 0 or 1, with the proviso that when m is 1, p is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more $-O-$ groups;

X'' is selected from the group consisting of $-\text{CH}(R_{13})\text{-alkylene-}$ and $-\text{CH}(R_{13})\text{-alkenylene-}$, wherein the alkylene and alkenylene are optionally interrupted by one or more $-O-$ groups;

Y is selected from the group consisting of:



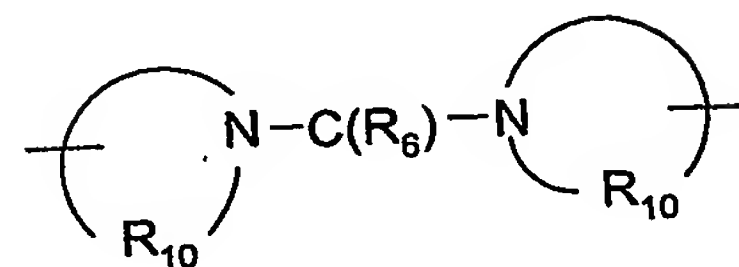
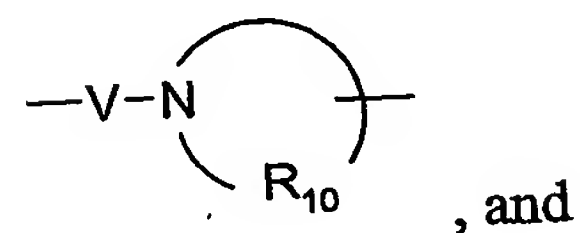
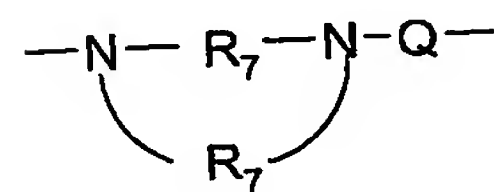
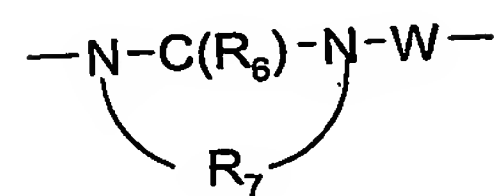
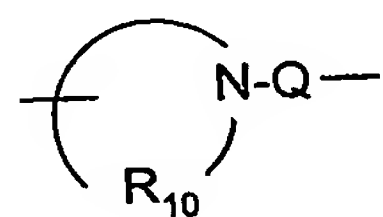
-O-C(O)-O-,

-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

-C(R₆)-N(OR₉)-,



Y' is selected from the group consisting of:

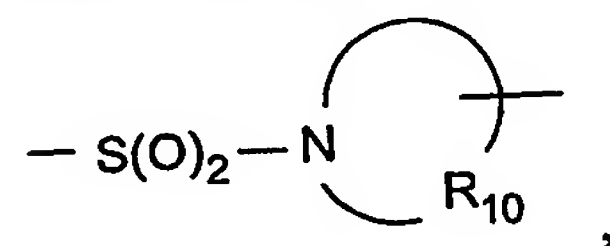
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

-S(O)₂-N(R₈)-,



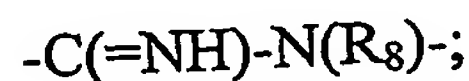
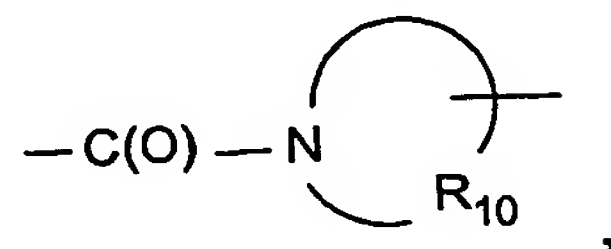
-C(O)-O-,

-C(O)-N(R₈)-,

-C(S)-N(R₈)-,

-C(O)-N(R₈)-S(O)₂-,

-C(O)-N(R₈)-C(O)-,

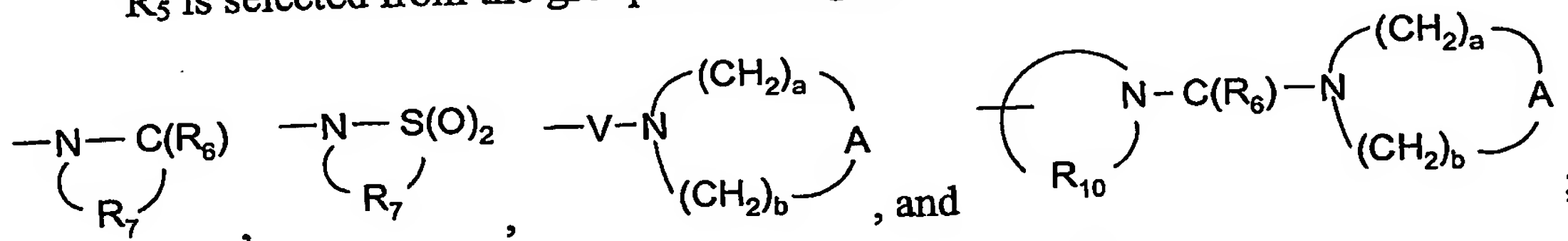


Z is a bond or -O-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

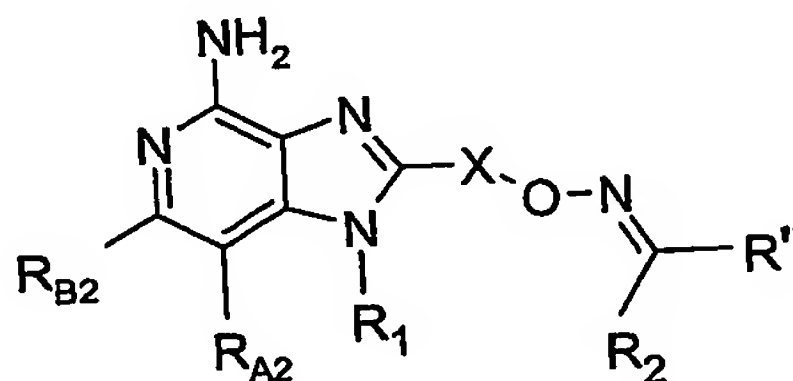
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

VI:



VI

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

R₁ is selected from the group consisting of:

-R₄,
-X'-R₄,
-X'-Y-R₄,
-X'-Y-X'-Y-R₄,
-X'-R₅,
-X''-O-NR_{1a}-Y'-R_{1b}, and
-X''-O-N=C(R₁') (R₁'');

R₂, R'', R_{1a}, R_{1b}, R₁', and R₁'' are independently selected from the group consisting

of:

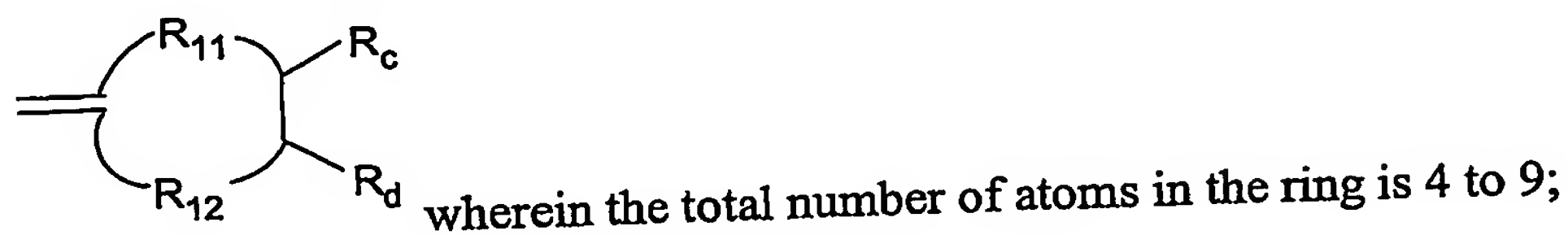
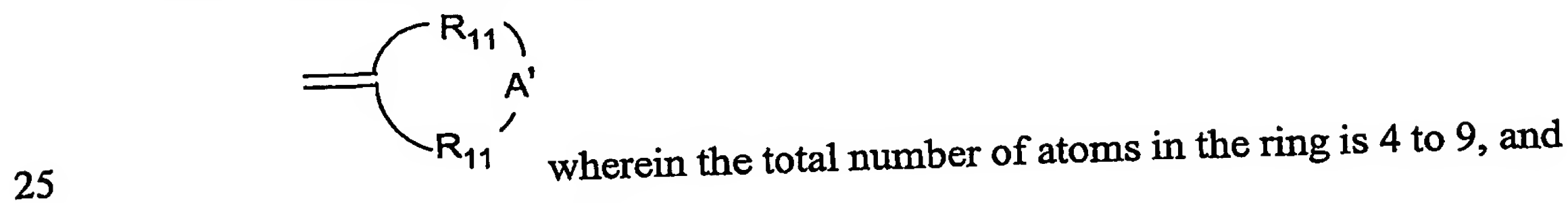
hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

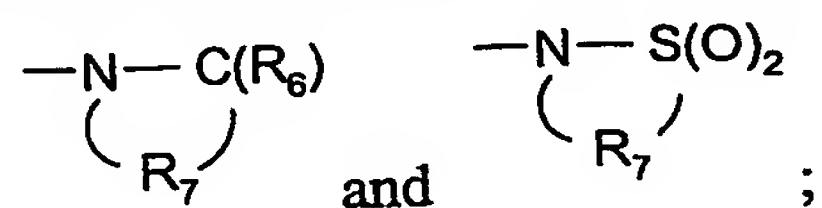
hydroxy,
alkyl,
haloalkyl,

hydroxyalkyl,
 alkoxy,
 amino,
 dialkylamino,
 5 -S(O)₀₋₂-alkyl,
 -S(O)₀₋₂-aryl,
 -NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 10 halogen,
 cyano,
 nitro,
 aryl,
 heteroaryl,
 15 heterocyclyl,
 aryloxy,
 arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 20 -N(R₈)-C(O)-alkyl,
 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₂ and R" and/or R₁' and R₁" can join together to form a ring system selected
 from the group consisting of:



or R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is selected from the group consisting of $-\text{CH}(\text{R}_{13})$ -alkylene- and $-\text{CH}(\text{R}_{13})$ -alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

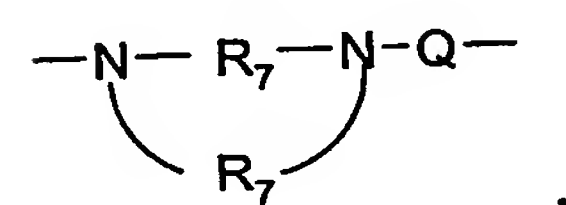
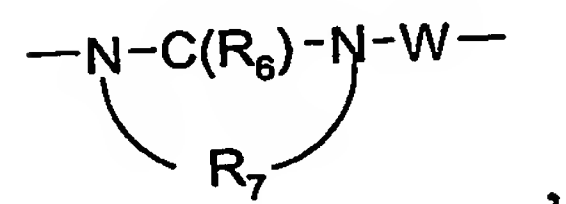
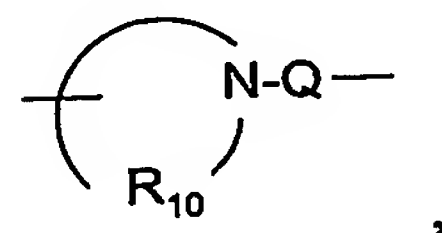
Y is selected from the group consisting of:

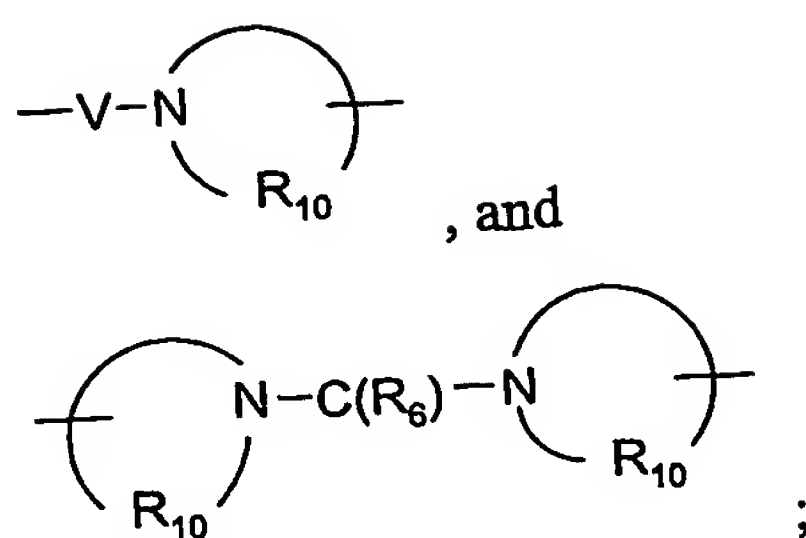
$$-S(O)_{0-2}-,$$
$$-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-,$$
$$-\text{C}(\text{R}_6)-,$$

15 $-\text{C}(\text{R}_6)-\text{O}-$,

$$-\text{O}-\text{C}(\text{R}_6)-,$$
$$-\text{O}-\text{C}(\text{O})-\text{O}-,$$
$$-N(R_8)-Q-$$
$$-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-,$$

20 $-O-C(R_6)-N(R_8)-$,

$$-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-,$$




Y' is selected from the group consisting of:

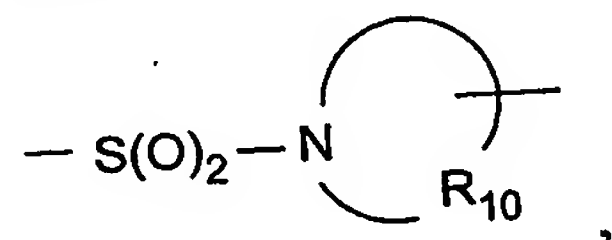
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

-S(O)₂-N(R₈)-,



-C(O)-O-,

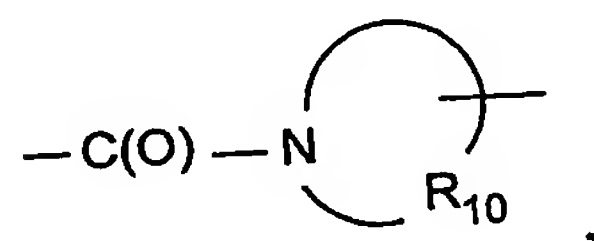
-C(O)-N(R₈)-,

-C(S)-N(R₈)-,

-C(O)-N(R₈)-S(O)₂-,

-C(O)-N(R₈)-C(O)-,

-C(S)-N(R₈)-C(O)-,



-C(O)-C(O)-,

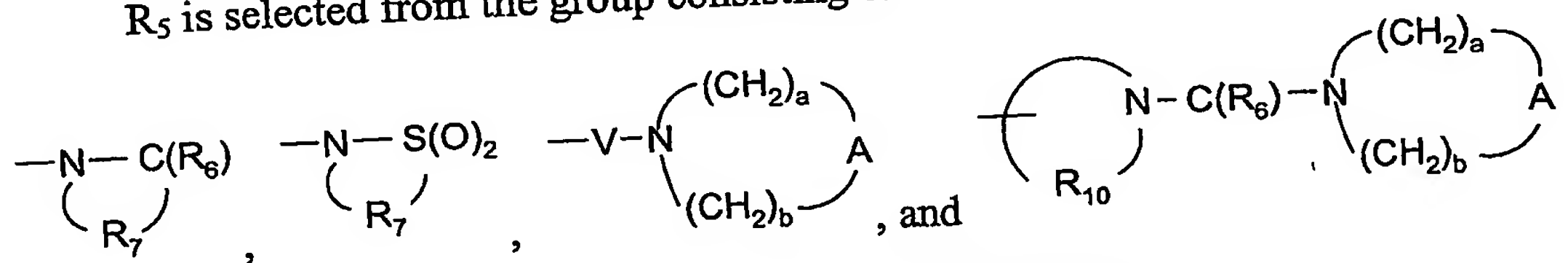
-C(O)-C(O)-O-, and

-C(=NH)-N(R₈)-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkyl, and aryl- C_{1-10} alkyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-\text{CH}_2-$, $-\text{O}-$, $-\text{C(O)}-$, $-\text{S(O)}_{0-2}-$, and $-\text{N(R}_4)-$;

A' is selected from the group consisting of $-\text{O}-$, $-\text{S(O)}_{0-2}-$, $-\text{N}(-\text{Q-R}_4)-$, and $-\text{CH}_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

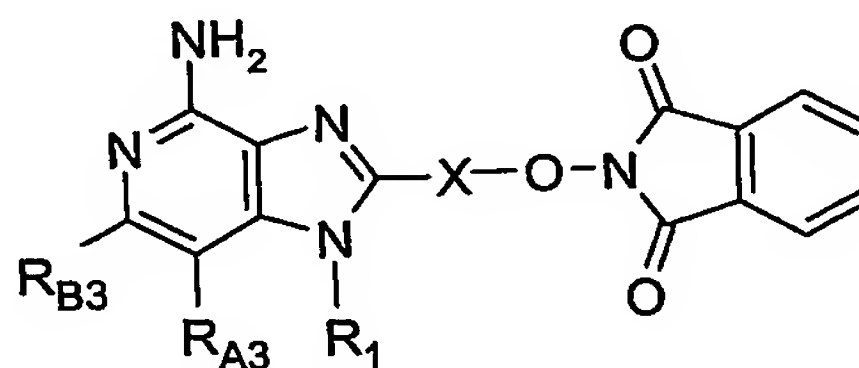
W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

VII:



VII

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_{A3} and R_{B3} , when taken together, form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A3} and R_{B3} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

R₁ is selected from the group consisting of:

-R₄,

-X'-R₄,

-X'-Y-R₄,

-X'-Y-X'-Y-R₄,

-X'-R₅,

-X''-O-NR_{1a}-Y'-R_{1b}, and

-X''-O-N=C(R_{1'})(R_{1''});

R_{1a}, R_{1b}, R_{1'}, and R_{1''} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

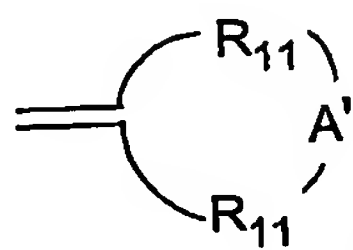
amino,

dialkylamino,

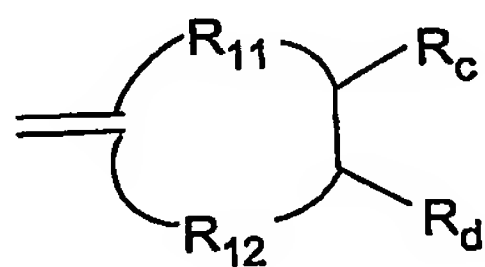
-S(O)₀₋₂-alkyl,

-S(O)₀₋₂-aryl,
 -NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 halogen,
 cyano,
 nitro,
 aryl,
 heteroaryl,
 heterocyclyl,
 aryloxy,
 arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 -N(R₈)-C(O)-alkyl,
 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₁' and R₁" can join together to form a ring system selected from the group consisting of:

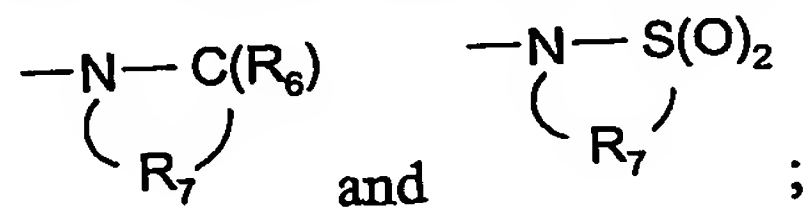


wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

or R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



R₃ is selected from the group consisting of:

-Z-R₄,

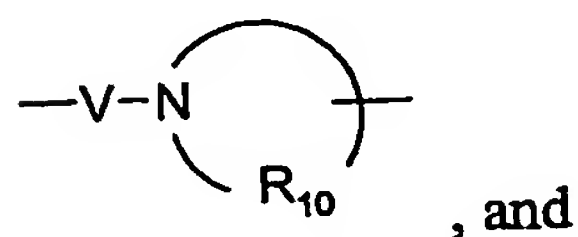
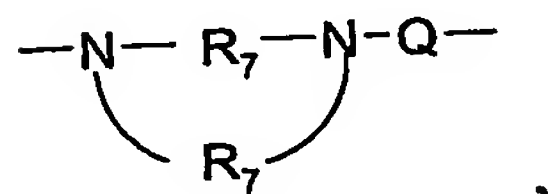
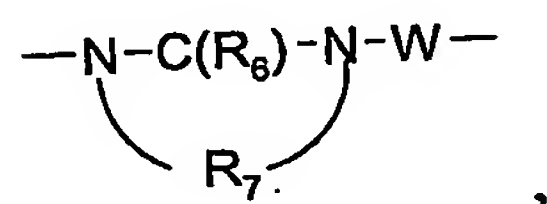
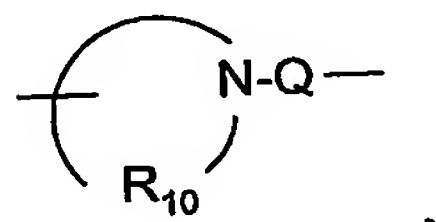
-Z-X'-R₄,
 -Z-X'-Y-R₄,
 -Z-X'-Y-X'-Y-R₄, and
 -Z-X'-R₅;

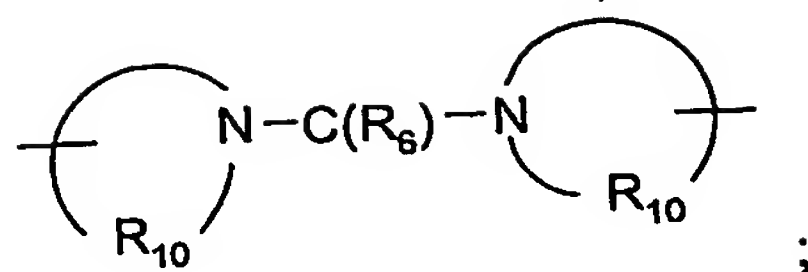
5 X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

10 X'' is selected from the group consisting of -CH(R₁₃)-alkylene- and -CH(R₁₃)-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 15 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 -O-C(O)-O-,
 -N(R₈)-Q-,
 20 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-,





Y' is selected from the group consisting of:

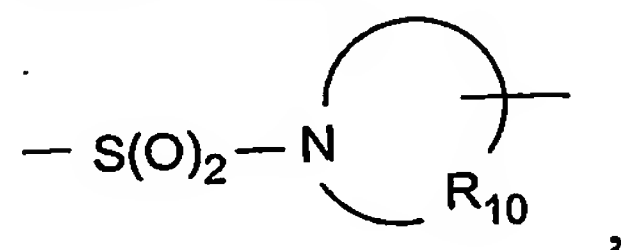
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

-S(O)₂-N(R₈)-,



-C(O)-O-,

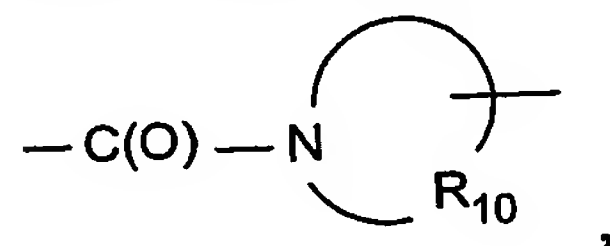
-C(O)-N(R₈)-,

-C(S)-N(R₈)-,

-C(O)-N(R₈)-S(O)₂-,

-C(O)-N(R₈)-C(O)-,

-C(S)-N(R₈)-C(O)-,



-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R₈)-;

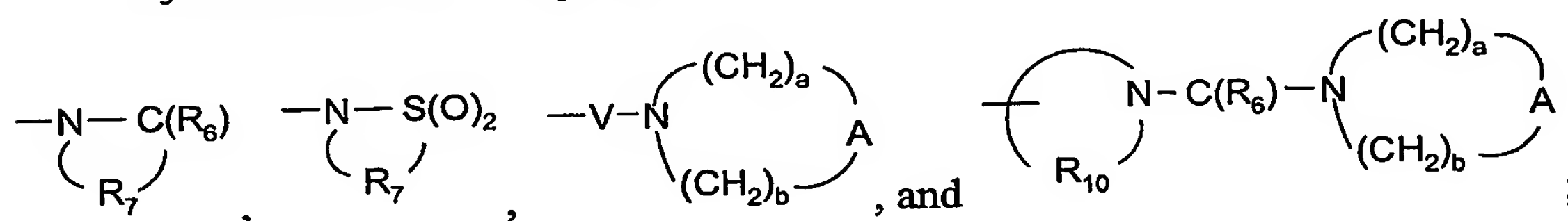
Z is a bond or -O-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

R₁₁ is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₂ is selected from the group consisting of a bond, C₁₋₅ alkylene, and C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₃ is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-\text{CH}_2-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_{0-2}-$, and $-\text{N}(\text{R}_4)-$;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and

-S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

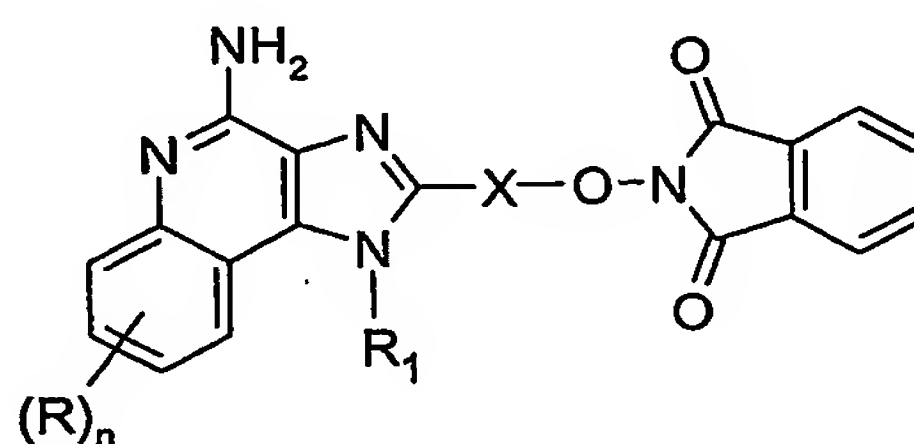
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

5

In one aspect, the present invention provides compounds of the following Formula

VIIa:



VIIa

10 wherein:

X is C₁₋₁₀ alkylene or C₂₋₁₀ alkenylene;

R is selected from the group consisting of:

halogen,

hydroxy,

15 alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

20 -N(R₉)₂;

R₁ is selected from the group consisting of:

-R₄,

-X'-R₄,

-X'-Y-R₄,

25 -X'-Y-X'-Y-R₄,

-X'-R₅,

-X''-O-NH-Y'-R₁', and

-X''-O-N=C(R₁') (R₁'');

R₁' and R₁" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

5 aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

10 heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

15 alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

20 -S(O)₀₋₂-alkyl,

-S(O)₀₋₂-aryl,

-NH-S(O)₂-alkyl,

-NH-S(O)₂-aryl,

haloalkoxy,

25 halogen,

cyano,

nitro,

aryl,

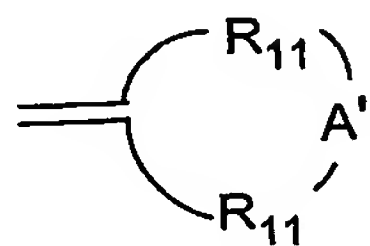
heteroaryl,

30 heterocyclyl,

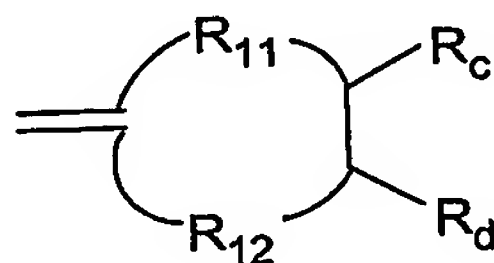
aryloxy,

arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 -N(R₈)-C(O)-alkyl,
 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₁' and R₁" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

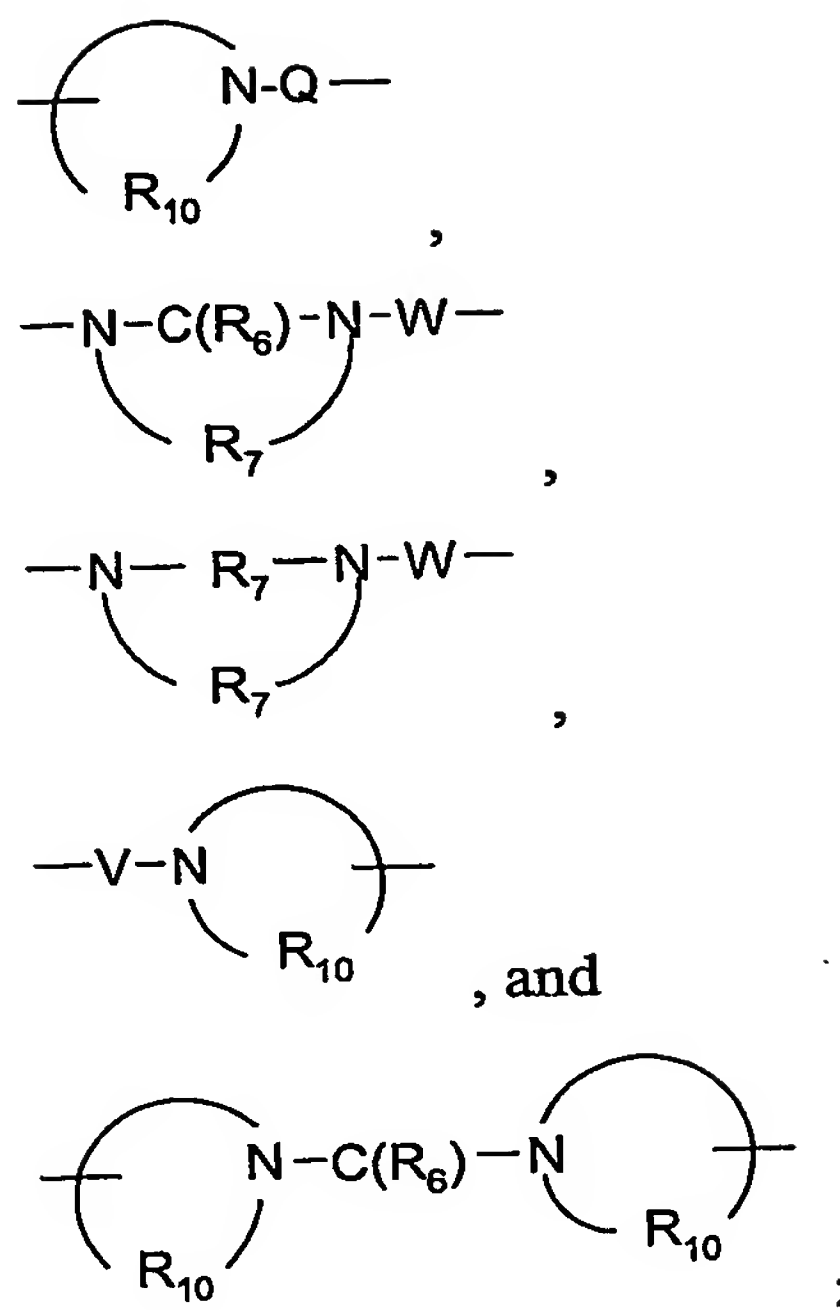
n is an integer from 0 to 4;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X'' is -CH(R₁₃)-alkylene- or -CH(R₁₃)-alkenylene-;

Y is selected from the group consisting of:

-S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 -O-C(O)-O-,
 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-,



5

Y' is selected from the group consisting of:

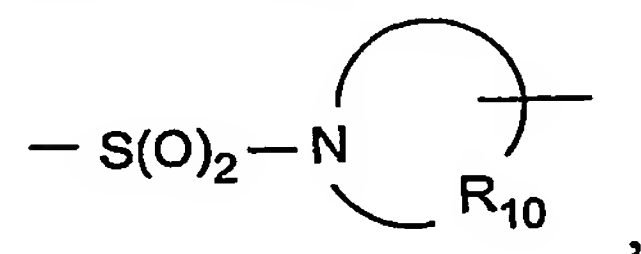
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

-S(O)₂-N(R₈)-,



-C(O)-O-,

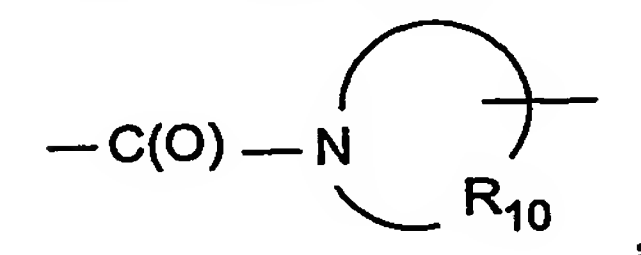
-C(O)-N(R₈)-,

-C(S)-N(R₈)-,

-C(O)-N(R₈)-S(O)₂-,

-C(O)-N(R₈)-C(O)-,

-C(S)-N(R₈)-C(O)-,



-C(O)-C(O)-,

10

15

20

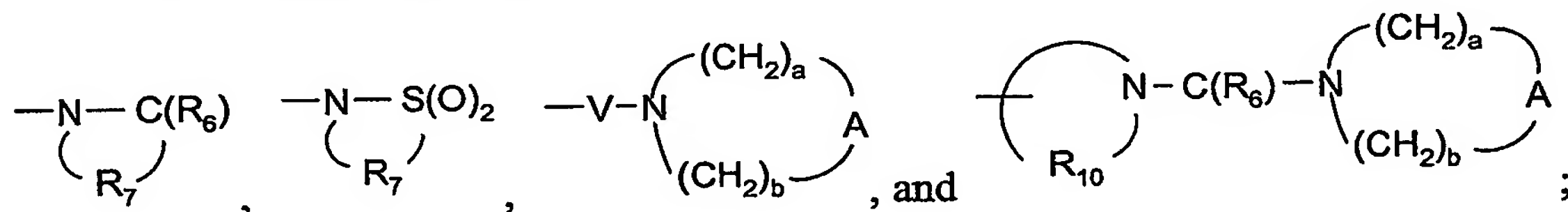
-C(O)-C(O)-O-, and

-C(=NH)-N(R₈)-;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

R₁₁ is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₂ is selected from the group consisting of a bond, C₁₋₅ alkylene, and

C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₃ is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

5 A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

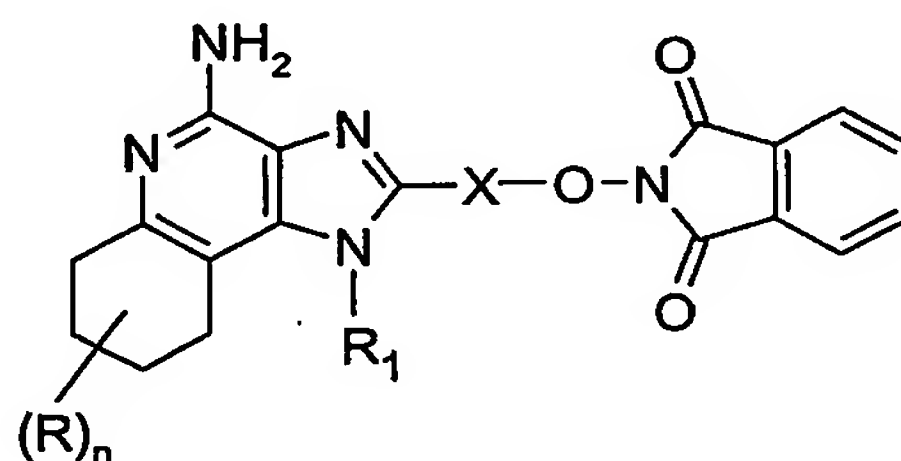
Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

10 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

15 In one aspect, the present invention provides compounds of the following Formula VIIb:



VIIb

20 wherein:

X is C₁₋₁₀ alkylene or C₂₋₁₀ alkenylene;

R is selected from the group consisting of:

halogen,

hydroxy,

25 alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_1 is selected from the group consisting of:

- 5 $-R_4$,
 $-X'-R_4$,
 $-X'-Y-R_4$,
 $-X'-Y-X'-Y-R_4$,
 $-X'-R_5$,
 10 $-X''-O-NH-Y'-R_1'$, and
 $-X''-O-N=C(R_1')(R_1'')$;

R_1' and R_1'' are independently selected from the group consisting of:

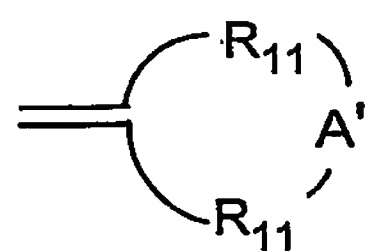
- hydrogen,
 alkyl,
 15 alkenyl,
 aryl,
 arylalkylenyl,
 heteroaryl,
 heteroarylalkylenyl,
 20 heterocyclyl,
 heterocyclylalkylenyl, and
 alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

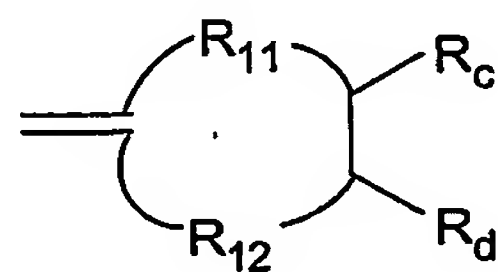
- 25 hydroxy,
 alkyl,
 haloalkyl,
 hydroxyalkyl,
 alkoxy,
 30 dialkylamino,
 $-S(O)_{0-2}$ -alkyl,

-S(O)₀₋₂-aryl,
 -NH-S(O)₂-alkyl,
 -NH-S(O)₂-aryl,
 haloalkoxy,
 halogen,
 cyano,
 nitro,
 aryl,
 heteroaryl,
 heterocyclyl,
 aryloxy,
 arylalkyleneoxy,
 -C(O)-O-alkyl,
 -C(O)-N(R₈)₂,
 -N(R₈)-C(O)-alkyl,
 -O-(CO)-alkyl, and
 -C(O)-alkyl;

or R₁' and R₁'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X'' is -CH(R₁₃)-alkylene- or -CH(R₁₃)-alkenylene-;

Y is selected from the group consisting of:

-S(O)₀₋₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

5

-O-C(R₆)-,

-O-C(O)-O-,

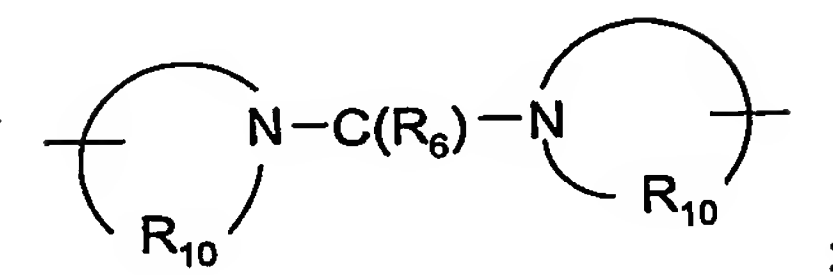
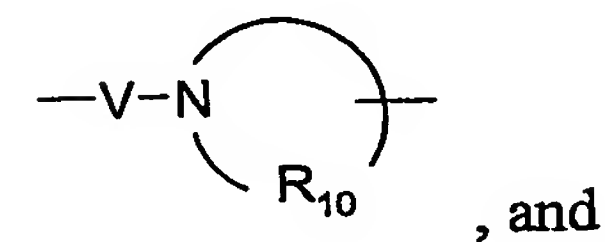
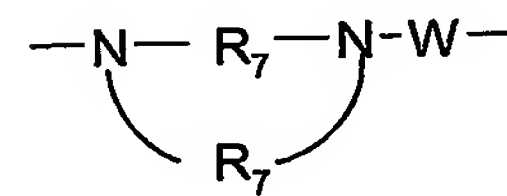
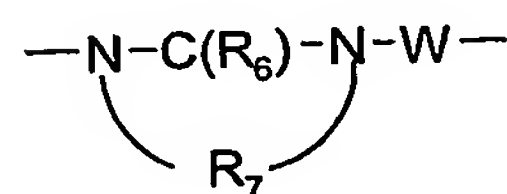
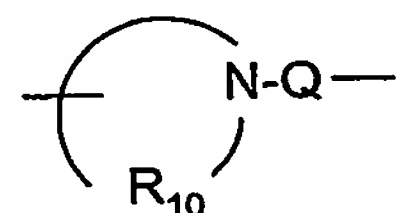
-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

10

-C(R₆)-N(OR₉)-,



15

Y' is selected from the group consisting of:

a bond,

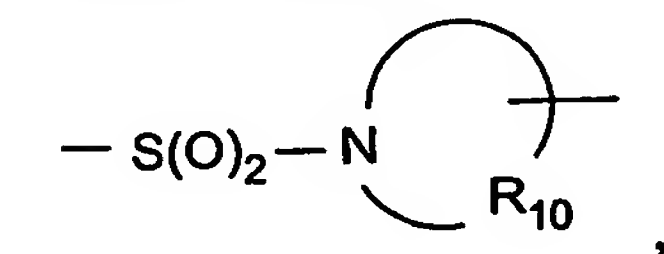
-C(O)-,

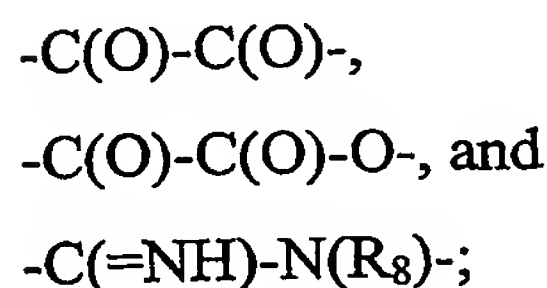
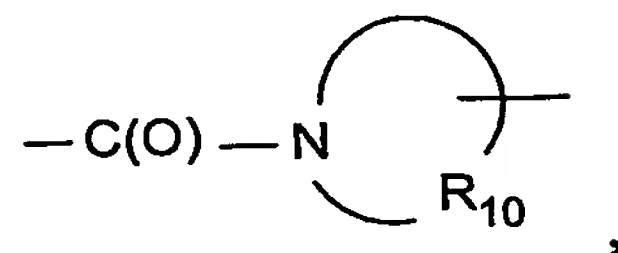
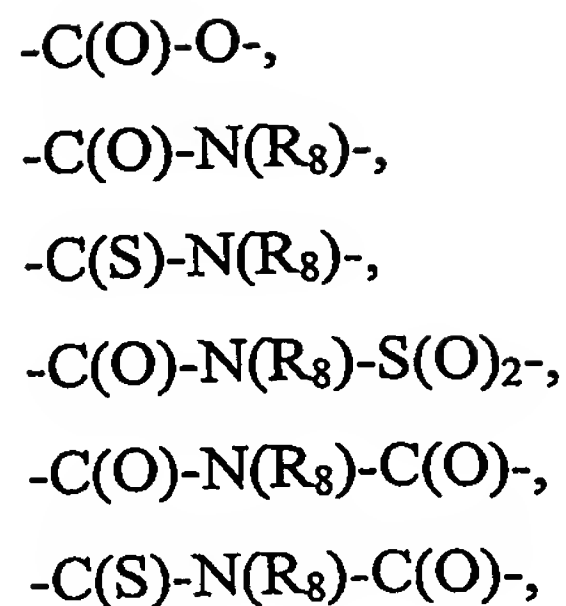
-C(S)-,

20

-S(O)₂-,

-S(O)₂-N(R₈)-,

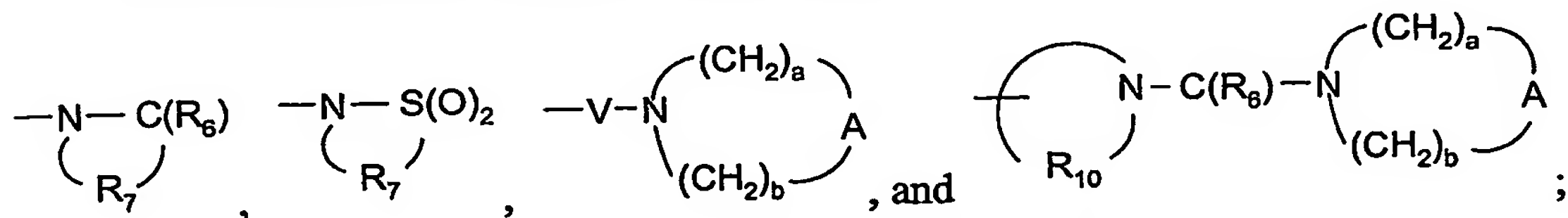




R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of $=O$ and $=S$;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

R₁₁ is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₂ is selected from the group consisting of a bond, C₁₋₅ alkylene, and C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R₁₃ is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

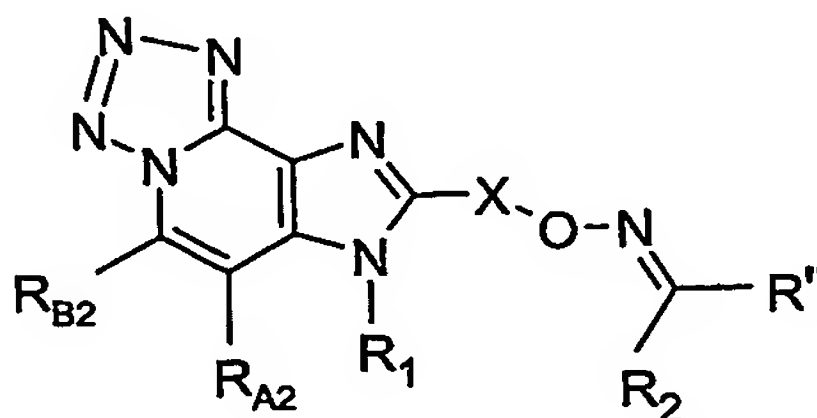
V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

In one aspect, the present invention provides compounds of the following Formula

VIII:



VIII

wherein:

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
 $-N(R_9)_2$;

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_1 is selected from the group consisting of:

$-R_4$,
 $-X'-R_4$,
 $-X'-Y-R_4$,
 $-X'-Y-X'-Y-R_4$,
 $-X'-R_5$,
 $-X''-O-NR_{1a}-Y'-R_{1b}$, and
 $-X''-O-N=C(R_1')(R_1'')$;

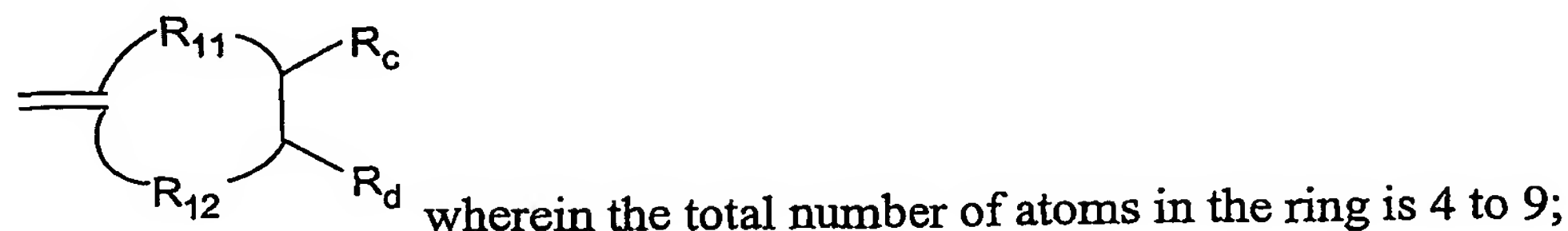
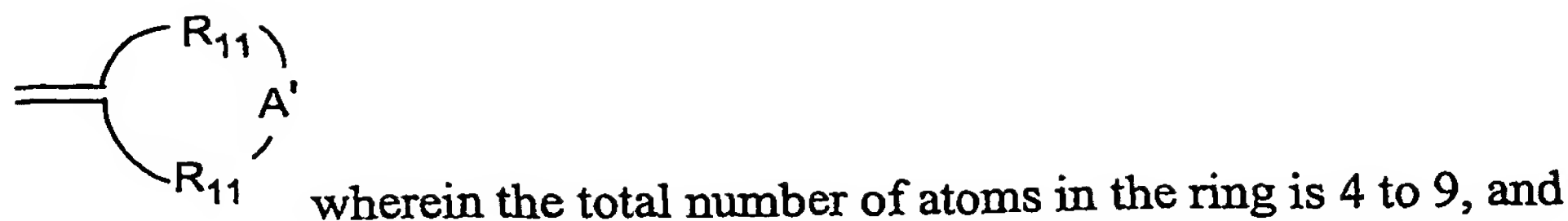
R_2 , R'' , R_{1a} , R_{1b} , R_1' , and R_1'' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

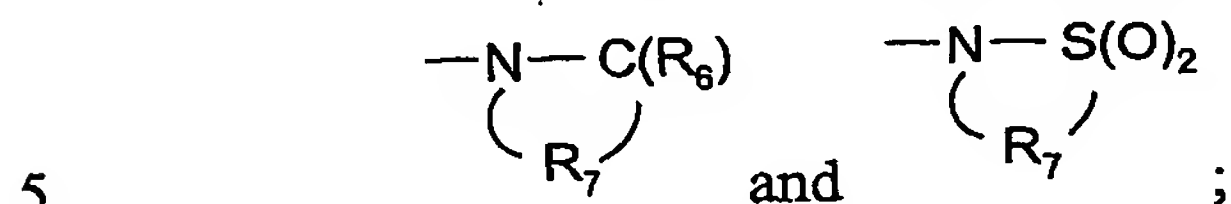
heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
5 alkoxy,
amino,
dialkylamino,
-S(O)₀₋₂-alkyl,
-S(O)₀₋₂-aryl,
10 -NH-S(O)₂-alkyl,
-NH-S(O)₂-aryl,
haloalkoxy,
halogen,
cyano,
15 nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
20 arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R₈)₂,
-N(R₈)-C(O)-alkyl,
-O-(CO)-alkyl, and
25 -C(O)-alkyl;

or R₂ and R'' and/or R₁' and R₁'' can join together to form a ring system selected from the group consisting of:



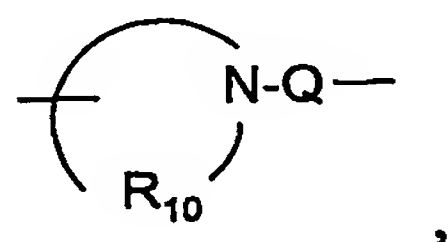
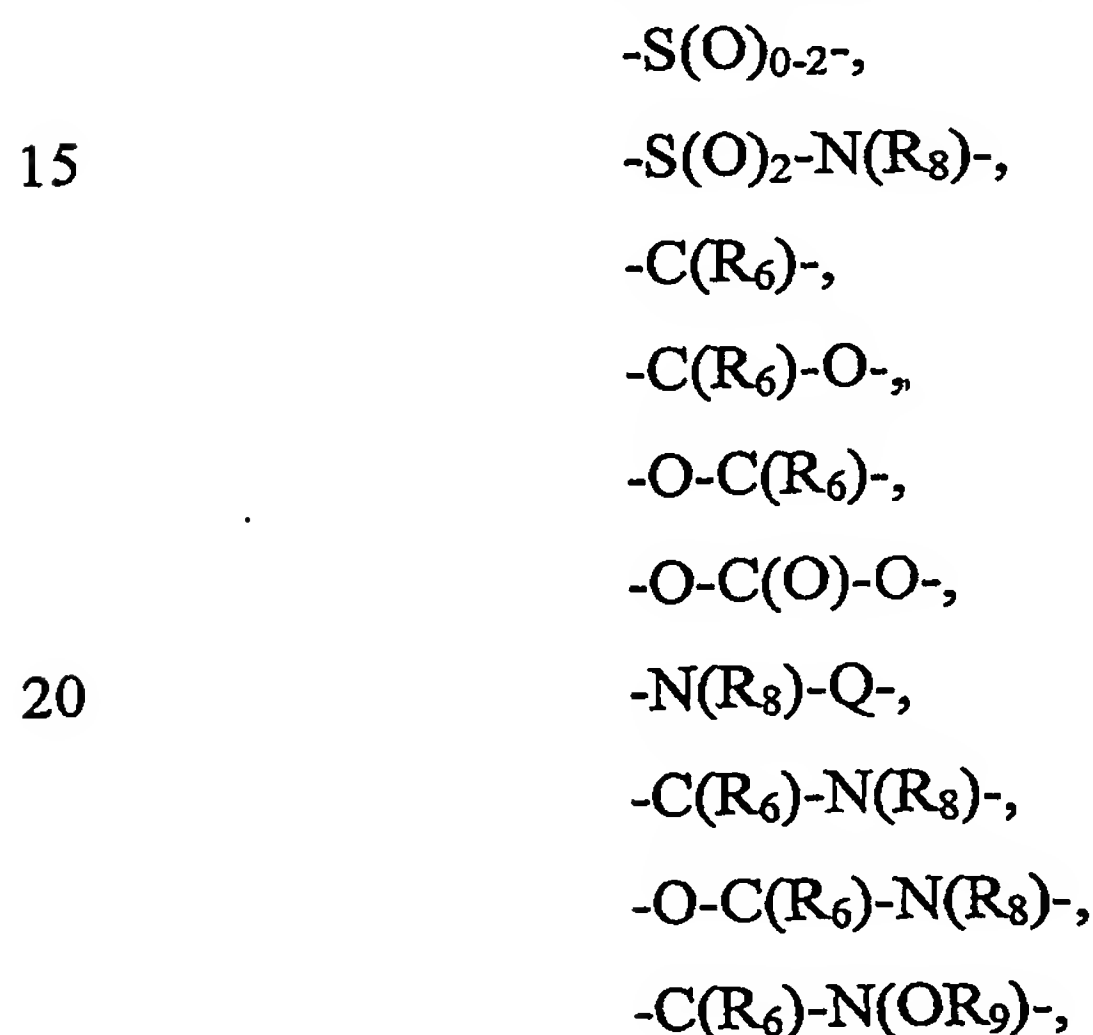
or R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

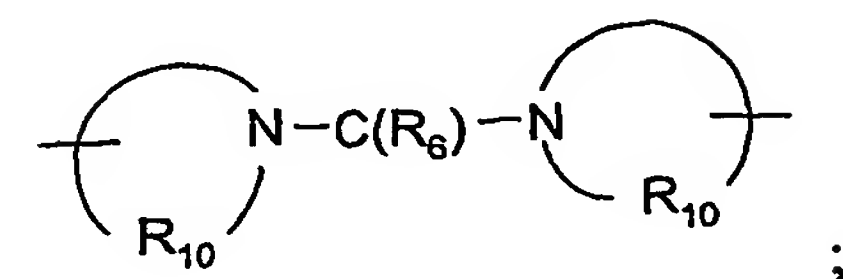
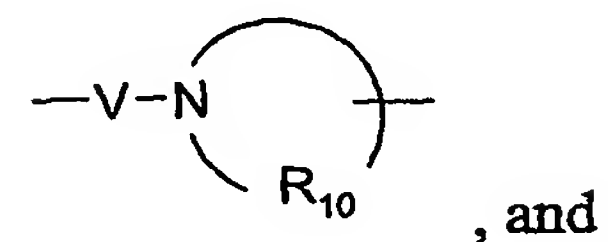
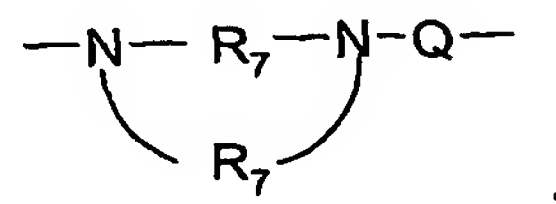
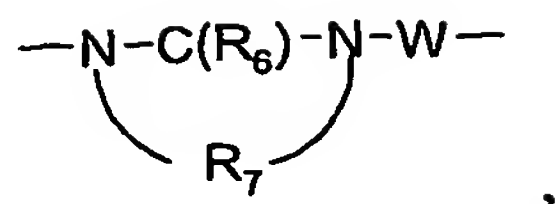


X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

10 X'' is selected from the group consisting of -CH(R₁₃)-alkylene- and -CH(R₁₃)-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:





5 Y' is selected from the group consisting of:

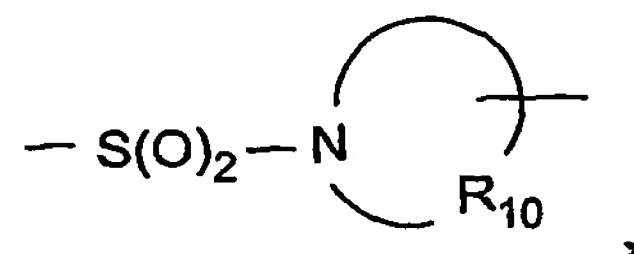
a bond,

-C(O)-,

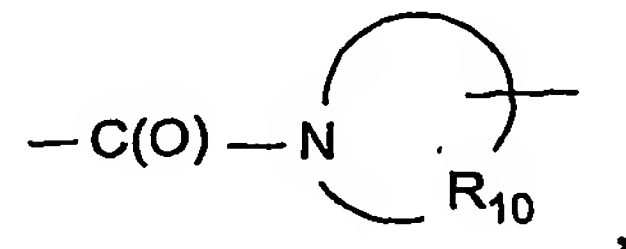
-C(S)-,

$$-\text{S}(\text{O})_2-$$

10 $-S(O)_2-N(R_8)-$,


$$-\text{C}(\text{O})-\text{O}-,$$
$$-\text{C}(\text{O})-\text{N}(\text{R}_8)-,$$
$$-\text{C}(\text{S})-\text{N}(\text{R}_8)-,$$

15 $-\text{C}(\text{O})-\text{N}(\text{R}_8)-\text{S}(\text{O})_2-$,

$$-\text{C}(\text{O})-\text{N}(\text{R}_8)-\text{C}(\text{O})-$$
$$-\text{C}(\text{S})-\text{N}(\text{R}_8)-\text{C}(\text{O})-$$


-C(O)-C(O)-,

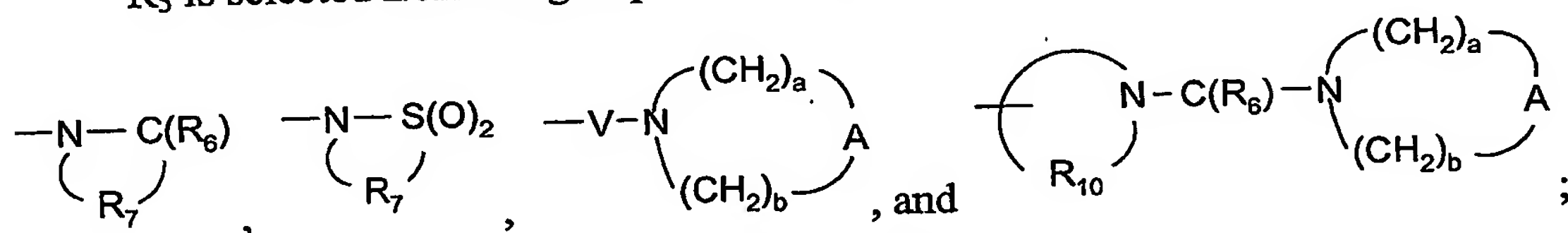
20 -C(O)-C(O)-O- , and

$$-\text{C}(=\text{NH})-\text{N}(\text{R}_8)-;$$

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

5 R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group
10 consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of $=O$ and $=S$;

R_7 is C_{2-7} alkylene;

20 R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

25 R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

5 A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

10 W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$; or a pharmaceutically acceptable salt thereof.

Certain embodiments of the present invention include non-interfering substituents. For example, in certain embodiments, R' is hydrogen or a non-interfering substituent, and in certain embodiments, R''' is a non-interfering substituent.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent. Illustrative non-interfering R' groups include those described herein for R_1 . Illustrative non-interfering R''' groups include those described herein for R and R_3 .

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, imidazoquinolinyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms,

“arylenyl”, “heteroarylenyl”, and “heterocyclylenyl” are used when “arylene,”
“heteroarylene,” and “heterocyclylene”, respectively, are substituted. For example, an
alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula
5 described herein, each group (or substituent or variable) is independently selected, whether
explicitly stated or not. For example, for the formula $-C(O)-N(R_8)_2$ each R_8 group is
independently selected. In another example, when an R_1 and an R_3 group both contain an
 R_4 group, each R_4 group is independently selected. In a further example, when more than
one Y group is present (i.e., R_1 and R_3 both contain a Y group) and each Y group contains
10 one or more R_7 groups, then each Y group is independently selected, and each R_7 group is
independently selected.

The invention is inclusive of the compounds described herein in any of their
pharmaceutically acceptable forms, including isomers (e.g., diastereomers and
enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is
15 optically active, the invention specifically includes each of the compound's enantiomers as
well as racemic mixtures of the enantiomers. It should be understood that the term
"compound" includes any or all of such forms, whether explicitly stated or not (although at
times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables
20 (e.g., R, R', R'', R_1 , R_2 , R_3 , R_A , R_B , R_{A1} , R_{B1} , R_{A2} , R_{B2} , R_{A3} , R_{B3} , n, m, p, X, Y, Y', Z, and
so on) in any of its embodiments can be combined with any one or more of the other
variables in any of their embodiments and associated with any one of the formulas
described herein, as would be understood by one of skill in the art. Each of the resulting
combinations of variables is an embodiment of the present invention.

25 In some embodiments, R is selected from the group consisting of halogen, hydroxy,
alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$. In some embodiments, R is
selected from the group consisting of halogen and hydroxy.

In some embodiments, R' is hydrogen or a non-interfering substituent. In some
embodiments, R' is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$,
30 $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NH-Y'-R_1'$, and $-X''-O-N=C(R_1')(R_1'')$. In some
embodiments, R' is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$,

$-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NR_{1a}-Y'-R_{1b}$, and $-X''-O-N=C(R_1')(R_1'')$.

In some embodiments, R_1 is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$, $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NR_{1a}-Y'-R_{1b}$, and $-X''-O-N=C(R_1')(R_1'')$.

In some embodiments, R_1 is selected from the group consisting of $-R_4$, $-X'-R_4$,
5 $-X'-Y-R_4$, $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NH-Y'-R_1'$, and $-X''-O-N=C(R_1')(R_1'')$.

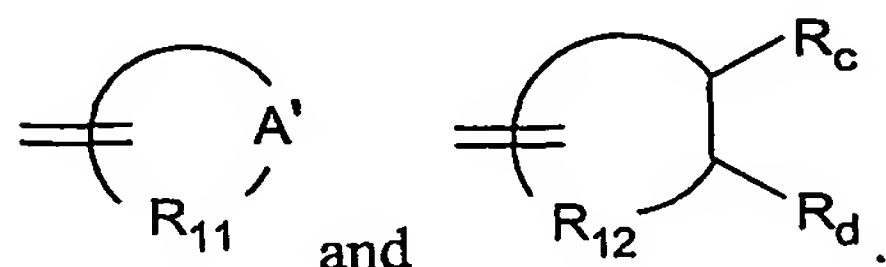
In some embodiments, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, $-X'-Y-R_4$, and $-X'-R_5$. In some embodiments, R_1 is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or $-X'-Y-R_4$. In some embodiments, R_1 is 2-methylpropyl or $-X'-Y-R_4$. In some
10 embodiments, R_1 is C_{1-6} alkyl or hydroxy- C_{1-6} alkyl. In some embodiments, R_1 is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or butyl. In some embodiments, R_1 is 2-methylpropyl or 2-hydroxy-2-methylpropyl. In some embodiments, R_1 is 2-methyl-2-[(methylsulfonyl)amino]propyl or 4-[(methylsulfonyl)amino]butyl.

In some embodiments, R_{1a} , R_{1b} , R_1' , and R_1'' are independently selected from the
15 group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, amino, dialkylamino, $-S(O)_{0-2}$ -alkyl, $-S(O)_{0-2}$ -aryl,
20 $-NH-S(O)_2$ -alkyl, $-NH-S(O)_2$ -aryl, haloalkoxy, halogen, cyano, nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, $-C(O)-O$ -alkyl, $-C(O)-N(R_8)_2$, $-N(R_8)-C(O)$ -alkyl, $-O-(CO)$ -alkyl, and $-C(O)$ -alkyl.

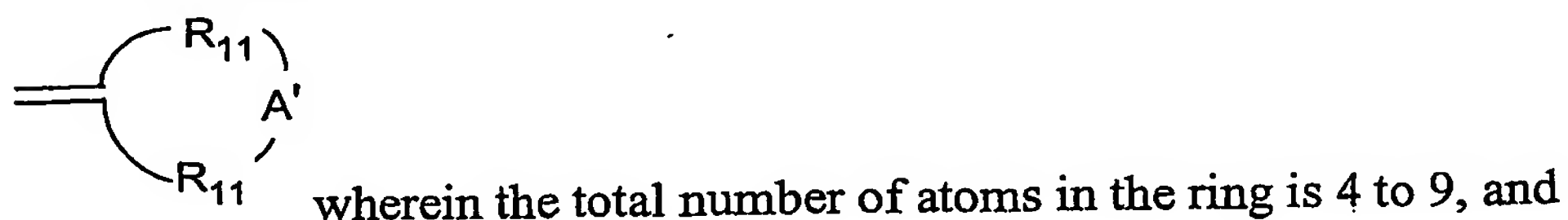
In some embodiments, R_{1a} , R_{1b} , R_1' , and R_1'' are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl,
25 heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, $-S(O)_{0-2}$ -alkyl, $-S(O)_{0-2}$ -aryl, $-NH-S(O)_2$ -alkyl, $-NH-S(O)_2$ -aryl, haloalkoxy, halogen, cyano, nitro, aryl, heteroaryl,
30 heterocyclyl, aryloxy, arylalkyleneoxy, $-C(O)-O$ -alkyl, $-C(O)-N(R_8)_2$, $-N(R_8)-C(O)$ -alkyl, $-O-(CO)$ -alkyl, and $-C(O)$ -alkyl.

In some embodiments, R_1' and R_1'' are the same as R_2 and R'' (discussed below).

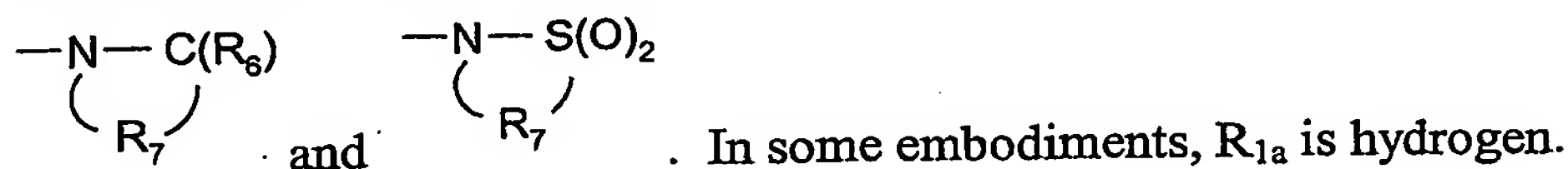
In some embodiments, R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



5 In some embodiments, R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



10 In some embodiments, R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

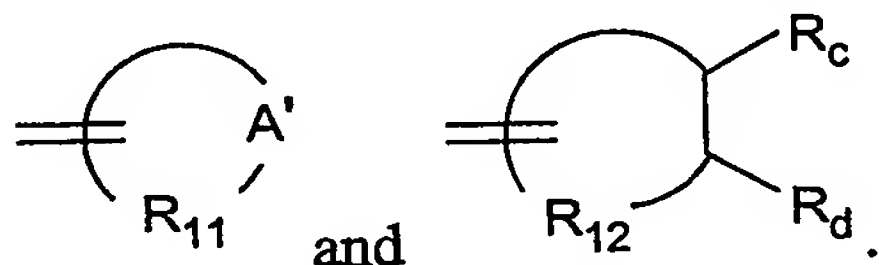


15 In some embodiments, R_2 and R'' are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy (i.e., hydroxyl), alkyl, haloalkyl, hydroxyalkyl, alkoxy, amino, dialkylamino, $-S(O)_{0-2}$ -alkyl, $-S(O)_{0-2}$ -aryl, $-NH-S(O)_2$ -alkyl, $-NH-S(O)_2$ -aryl, haloalkoxy, halogen, cyano (i.e., nitrile), nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, $-C(O)-O$ -alkyl, $-C(O)-N(R_8)_2$, $-N(R_8)-C(O)$ -alkyl, $-O-(CO)$ -alkyl, and $-C(O)$ -alkyl. Herein, for certain embodiments, this list of substituents is being referenced when an R_2 or R'' group is referred to as substituted or optionally substituted.

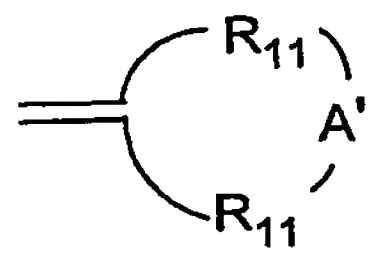
20 In some embodiments, R_2 and R'' are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy (i.e., hydroxyl), alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, $-S(O)_{0-2}$ -alkyl, $-S(O)_{0-2}$ -aryl, $-NH-S(O)_2$ -alkyl, $-NH-S(O)_2$ -aryl, haloalkoxy, halogen, cyano (i.e., nitrile), nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, $-C(O)-O$ -alkyl, $-C(O)-N(R_8)_2$, $-N(R_8)-C(O)$ -alkyl, $-O-(CO)$ -alkyl, and $-C(O)$ -alkyl. Herein, for certain embodiments, this list of substituents is being referenced when an R_2 or R'' group is referred to as substituted or optionally substituted.

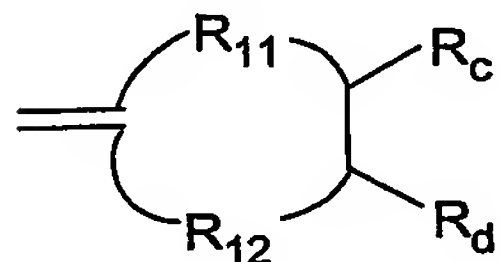
In some embodiments, R_2 and R'' can join together to form a ring system. In some embodiments, the ring system is selected from the group consisting of:



Preferably the ring system is selected from the group consisting of:

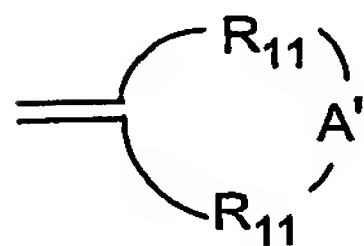


wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9.

In some embodiments, the ring system is



In some embodiments, R'' or R_2 is selected from the group consisting of alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, and heterocyclylalkylenyl are optionally substituted (by this it is meant, substituted by the groups listed above as possible substituents for R_2 and R''). In some embodiments, at least one of R'' or R_2 is alkyl or substituted alkyl. In some

embodiments, at least one of R" or R₂ is alkenyl or substituted alkenyl. In some
embodiments, at least one of R" or R₂ is aryl, arylalkylenyl, substituted aryl, or substituted
arylalkylenyl. In some embodiments at least one of R" or R₂ is heteroaryl,
heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl. In some
5 embodiments, at least one of R" or R₂ is heterocyclyl, heterocyclylalkylenyl, substituted
heterocyclyl, or substituted heterocyclylalkylenyl.

In some embodiments, R₂ is selected from the group consisting of alkyl, alkenyl,
aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, and heterocyclylalkylenyl,
wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl,
10 and heterocyclylalkylenyl are optionally substituted (by this it is meant, substituted by the
groups listed above as possible substituents for R₂). In some embodiments, R₂ is alkyl or
substituted alkyl. In some embodiments, R₂ is alkenyl or substituted alkenyl. In some
embodiments, R₂ is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl. In
some embodiments, R₂ is heteroaryl, heteroarylalkylenyl, substituted heteroaryl, or
15 substituted heteroarylalkylenyl. In some embodiments, R₂ is heterocyclyl,
heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl.

In some embodiments, at least one of R" or R₂ is selected from the group
consisting of methyl, ethyl, cyclopropyl, 2-(ethoxycarbonyl)cyclopropyl, propyl, butyl, 2-
methylpropyl, *tert*-butyl, cyclopentyl, 2-cyclopentylethyl, acetoxymethyl,
20 (ethoxycarbonyl)methyl, furyl, furfuryl, cyclohexyl, tetrahydrofuranyl, 2-(methylthio)ethyl,
phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-
methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl,
4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-
cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-
25 acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-trifluoromethylphenyl, phenylmethyl,
phenoxymethyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethenyl, biphenyl, 2-pyridyl, 3-
pyridyl, 4-pyridyl, 1-methylpyrrol-2-yl, 1-methylimidazol-2-yl, 1-methylimidazol-4-yl, 3-
cyclohexen-1-yl, 3,4-dihydro-2*H*-pyran-2-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl,
thiazol-2-yl, 5-isoxazolyl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, 1-methylindol-2-yl,
30 1-methylindol-3-yl, hydroxymethyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 3,4-

dichlorophenyl, 4-hydroxyphenyl, 2-hydroxyethyl, 1-hydroxyethyl, 2-hydroxy-2-methylpropyl, heptyl, and pyrrol-3-yl.

In some embodiments, at least one of R" or R₂ is selected from the group consisting of methyl, ethyl, cyclopropyl, 2-(ethoxycarbonyl)cyclopropyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, cyclopentyl, 2-cyclopentylethyl, acetoxymethyl, (ethoxycarbonyl)methyl, furyl, furfuryl, cyclohexyl, tetrahydrofuranyl, 2-(methylthio)ethyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-trifluoromethylphenyl, phenylmethyl, phenoxyethyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethenyl, biphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-methylpyrrol-2-yl, 1-methylimidazol-2-yl, 1-methylimidazol-4-yl, 3-cyclohexen-1-yl, 3,4-dihydro-2*H*-pyran-2-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, 5-isoxazolyl, and quinolin-2-yl.

In some embodiments, R₂ and R" are independently C₁₋₁₀ alkyl. In some embodiments, at least one of R" or R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl. In some embodiments, R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl. In some embodiments, R₂ and R" are each methyl.

In some embodiments, at least one of R" or R₂ is hydrogen. In some embodiments, particularly embodiments of Formulas IIIa and IVa, R" is hydrogen.

In some embodiments, R₂ is C₁₋₄ alkyl. In some embodiments, R" is hydrogen or C₁₋₄ alkyl. In some embodiments, R" is C₁₋₄ alkyl. In some embodiments, R₂ is hydrogen or C₁₋₄ alkyl.

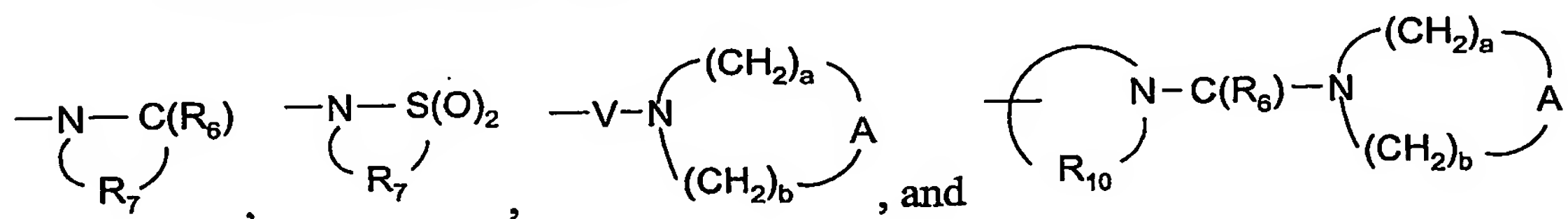
In some embodiments, R''' is a non-interfering substituent. In some embodiments, R''' is R₃. In some embodiments, particularly embodiments of Formula III, R''' is R or R₃ when n is 1, R or one R and one R₃ when n is 2, or R when n is 3 to 4.

In some embodiments, R₃ is selected from the group consisting of -Z-R₄, -Z-X'-R₄, -Z-X'-Y-R₄, -Z-X'-Y-X'-Y-R₄, and -Z-X'-R₅. In some embodiments, R₃ is selected from the group consisting of -Z-R₄ and -Z-X'-Y-R₄.

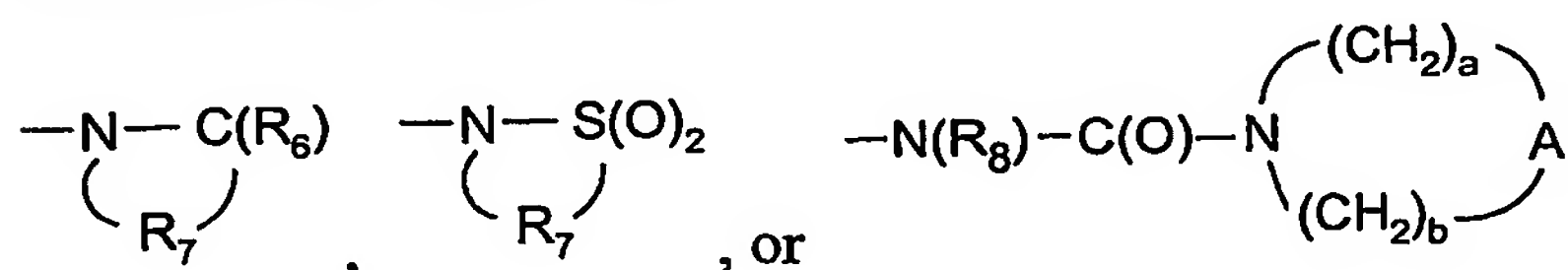
In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

In some embodiments, R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl. In some embodiments, R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl, wherein alkyl and alkenyl are optionally substituted by aryl or aryloxy and wherein aryl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, cyano, and halogen. In some embodiments, R_4 is alkyl or arylalkylenyl. In some embodiments, R_4 is selected from the group consisting of aryl or heteroaryl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, hydroxy, cyano, hydroxyalkyl, dialkylamino, and alkoxy.

In some embodiments, R_5 is selected from the group consisting of:



In some embodiments, R_5 is



In some embodiments, R_6 is selected from the group consisting of =O and =S. In some embodiments, R_6 is =O.

In some embodiments, R_7 is C_{2-7} alkylene. In some embodiments, R_7 is ethylene. In some embodiments, R_7 is propylene.

In some embodiments, R_8 is selected from the group consisting of hydrogen,

C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl. In some embodiments, R₈ is hydrogen or methyl. In some embodiments, R₈ is hydrogen.

In some embodiments, R₉ is selected from the group consisting of hydrogen and alkyl.

5 In some embodiments, R₁₀ is C₃₋₈ alkylene. In some embodiments, R₁₀ is pentylene.

In some embodiments, R₁₁ is C₃₋₉ alkylene or C₃₋₉ alkenylene, optionally interrupted by one hetero atom. In some embodiments, R₁₁ is C₁₋₆ alkylene or C₂₋₆ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom.

10 In some embodiments, R₁₁ is C₁₋₂ alkylene. In some embodiments, R₁₁ is methylene; in some embodiments, R₁₁ is ethylene.

In some embodiments, R₁₂ is C₂₋₇ alkylene or C₂₋₇ alkenylene, optionally interrupted by one hetero atom. In some embodiments, R₁₂ is selected from the group consisting of a bond, C₁₋₅ alkylene, and C₂₋₅ alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom. In some embodiments, R₁₂ is ethylene.

15 In some embodiments, R₁₃ is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups. In some embodiments, R₁₃ is hydrogen.

In some embodiments, R_A and R_B are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R₉)₂; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In some embodiments, particularly embodiments of Formula I, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R₉)₂.

30 In some embodiments, particularly embodiments of Formula I, R_A and R_B form a fused aryl or heteroaryl ring.

In some embodiments, particularly embodiments of Formula I, R_A and R_B form a fused 5 to 7 membered saturated ring.

5 In some embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group; or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom
10 selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In some embodiments, particularly embodiments of Formula II, R_{A1} and R_{B1} form a fused benzene ring which is unsubstituted.

15 In some embodiments, particularly embodiments of Formula II, R_{A1} and R_{B1} form a fused pyridine ring which is unsubstituted.

In some embodiments, particularly embodiments of Formula II, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted. In certain of these embodiments the fused saturated ring is a cyclohexene ring.

20 In some embodiments, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. In certain of these embodiments, R_{A2} and R_{B2} are each independently alkyl. In some embodiments, R_{A2} and R_{B2} are each methyl.

25 In some embodiments, R_{A3} and R_{B3} , when taken together, form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group; or when taken together, R_{A3} and R_{B3} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and
30 unsubstituted or substituted by one or more R groups.

In some embodiments, R_{A3} and R_{B3} form a fused benzene ring which is unsubstituted.

In some embodiments, R_{A3} and R_{B3} form a fused pyridine ring which is unsubstituted.

5 In some embodiments, R_{A3} and R_{B3} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted. In certain of these embodiments the fused saturated ring is a cyclohexene ring.

10 In some embodiments, R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms. In some embodiments, at least one of R_c or R_d is aryl.

15 In some embodiments, A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(R_4)-$. In some embodiments, A is selected from the group consisting of $-CH_2-$ and $-O-$.

In some embodiments, A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$. In some embodiments, A' is $-CH_2-$, $-O-$, or $-N(-Q-R_4)-$. In some embodiments, A' is $-CH_2-$ or $-N(-Q-R_4)-$. In some embodiments, A' is $-CH_2-$.

20 In some embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$. In some embodiments, Q is a bond or $-C(O)-$. In some embodiments, Q is selected from the group consisting of $-C(O)-$, $-S(O)_2-$, and $-C(O)-N(R_8)-W-$.

25 In some embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$. In some embodiments, V is $-N(R_8)-C(O)-$.

In some embodiments, W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$. In some embodiments, W is selected from the group consisting of a bond and $-C(O)-$.

30 In some embodiments, X is C_{1-10} alkylene or C_{2-10} alkenylene. Preferably, X is C_{1-10} alkylene or C_{3-10} alkenylene. In some embodiments, particularly embodiments of Formulas IIIa and IVa, X is C_{1-4} alkylene. In some embodiments, X is methylene.

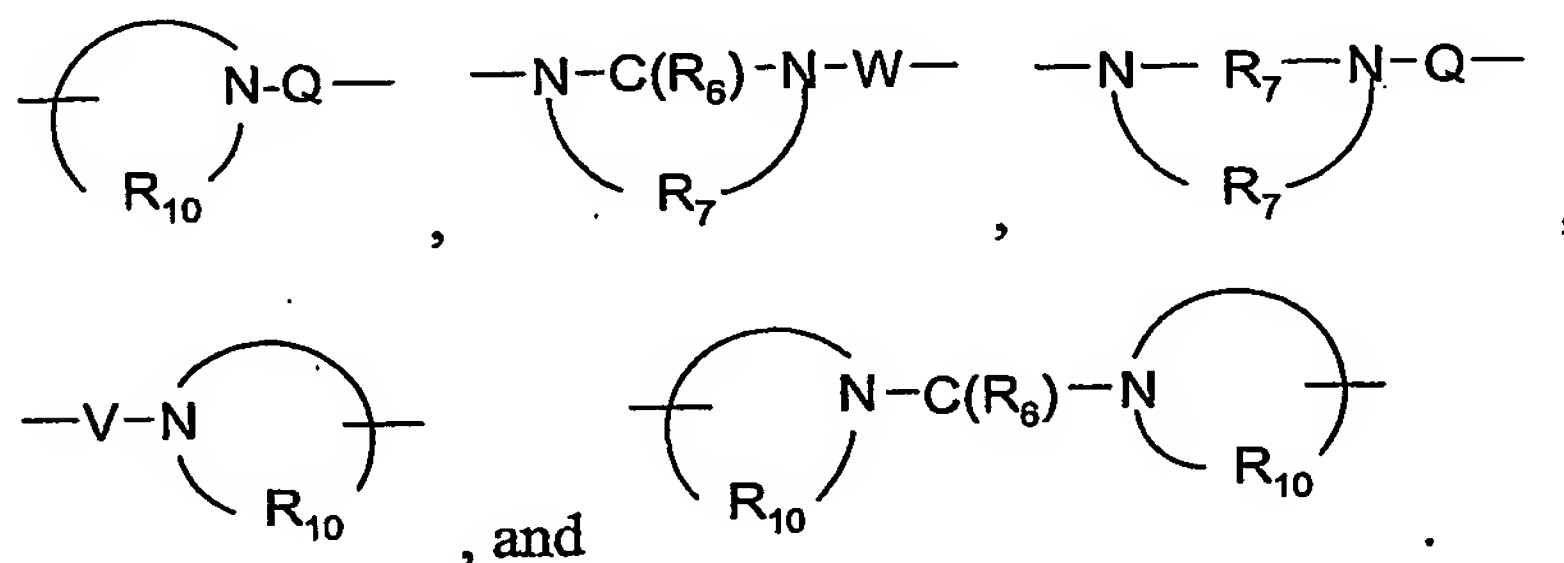
In some embodiments, particularly embodiments of Formula IIIa and IVa, X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups. In some

5 embodiments, X' is alkylene. In some embodiments, X' is ethylene, propylene, or butylene (including isobutylene).

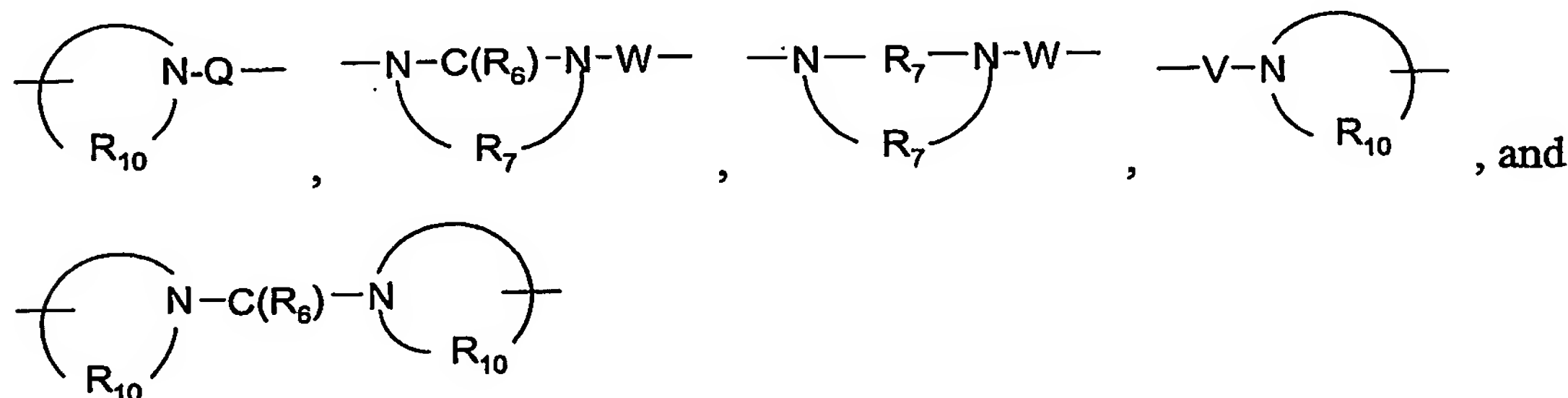
In some embodiments, X'' is selected from the group consisting of -CH(R₁₃)-alkylene- and -CH(R₁₃)-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups. In some embodiments, particularly in

10 embodiments of Formula IIIa and IVa, X'' is -CH(R₁₃)-alkylene- or -CH(R₁₃)-alkenylene-.

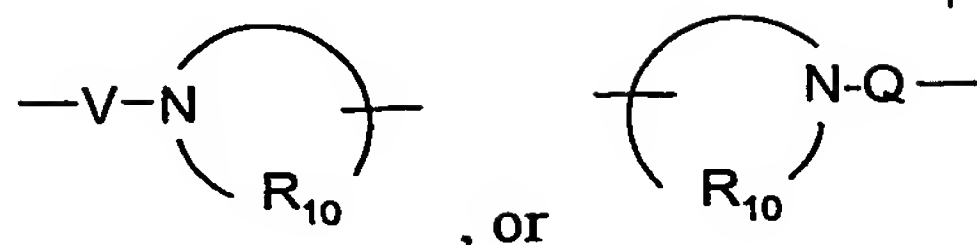
In some embodiments, Y is selected from the group consisting of -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-,



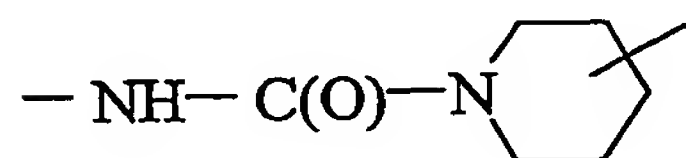
In some embodiments, Y is selected from the group consisting of -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-,



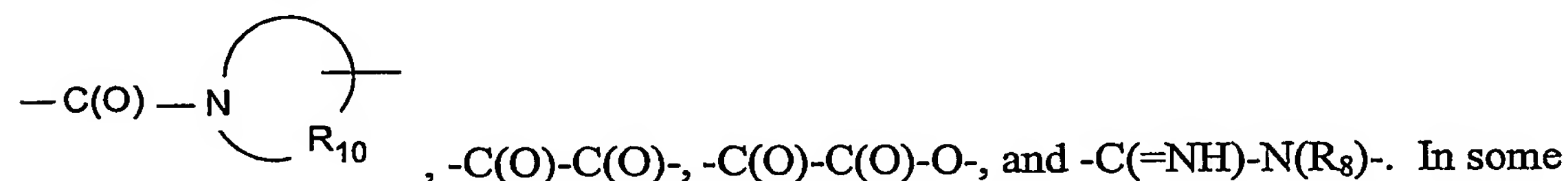
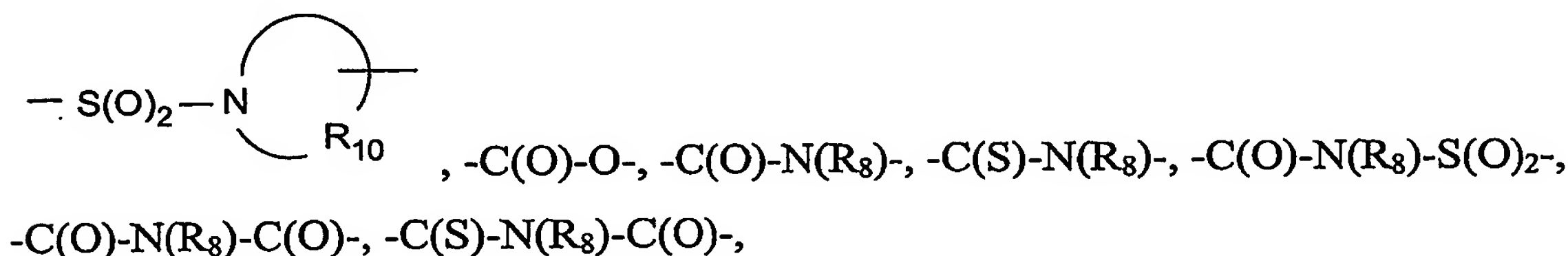
In some embodiments, Y is -N(R₈)-C(O)-, -N(R₈)-S(O)₂-, -N(R₈)-S(O)₂-N(R₈)-, -N(R₈)-C(O)-N(R₈)-, -N(R₈)-C(O)-N(R₈)-C(O)-,



In some embodiments, Y is -NH-C(O)-, -NH-S(O)₂-, -NH-S(O)₂-N(R₈)-, -NH-C(O)-N(R₈)-, -NH-C(O)-NH-C(O)-, or



5 In some embodiments, Y' is selected from the group consisting of a bond, -C(O)-, -C(S)-, -S(O)₂-, -S(O)₂-N(R₈)-,



10 In some embodiments, Y' is selected from the group consisting of -C(O)-, -S(O)₂-, and -C(O)-N(R₈)-.

In some embodiments, Z is a bond or Z is a bond or -O-. In some embodiments, Z is a bond. In some embodiments, Z is -O-.

15 In some embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7. In some embodiments, a and b are each 2.

In some embodiments, n is an integer from 0 to 4. In some embodiments, n is 0 or 1. In some embodiments, particularly embodiments of Formula IVa, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3 or 4.

20 In some embodiments m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1.

In some embodiments, p is an integer from 0 to 3. In some embodiments, p is 0 or 1. In some embodiments p is 0.

In some embodiments, particularly embodiments of Formula IIIa, both n and m are 0. In some embodiments, particularly embodiments of Formula V, both m and p are 0.

25 In some embodiments, n is 0, m is 0, or both n and m are 0.

In some embodiments, particularly embodiments of Formula IIIa, m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1.

In some embodiments, particularly embodiments of Formula V, m is 0 or 1, with the proviso that when m is 1, p is 0 or 1.

5 In some embodiments, X is C₁₋₄ alkylene; R₂ is C₁₋₄ alkyl; R" is hydrogen or C₁₋₄ alkyl; and R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl.

In some embodiments, X is C₁₋₄ alkylene; R" is C₁₋₄ alkyl; R₂ is hydrogen or C₁₋₄ alkyl; and R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl.

10 In some embodiments, X is methylene; at least one of R" or R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl; and R₁ is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or butyl.

In some embodiments, X is methylene; R" and R₂ are methyl; and R₁ is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

15 In some embodiments, X is C₁₋₄ alkylene; R" is C₁₋₄ alkyl; R₂ is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and n and m are 0.

In some embodiments, particularly embodiments of Formula IIIa, X is C₁₋₄ alkylene; R" is hydrogen or C₁₋₄ alkyl; R₂ is C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and n and m are 0.

20 In some embodiments, particularly embodiments of Formula VI, X is C₁₋₄ alkylene; R₂ is C₁₋₄ alkyl; R" is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and R_{A2} and R_{B2} are each methyl.

In some embodiments, particularly embodiments of Formula VI, X is C₁₋₄ alkylene; R" is C₁₋₄ alkyl; R₂' is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and R_{A2} and R_{B2} are each methyl.

25 In some embodiments, particularly embodiments of Formula V, X is C₁₋₄ alkylene; R₂ is C₁₋₄ alkyl; R" is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and p and m are 0.

In some embodiments, X is C₁₋₄ alkylene; R₂ is C₁₋₄ alkyl; R" is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and n is 0.

30 In some embodiments, particularly embodiments of Formula V, X is C₁₋₄ alkylene; R" is C₁₋₄ alkyl; R₂ is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or

hydroxy-C₁₋₆ alkyl; and p and m are 0.

In some embodiments, X is C₁₋₄ alkylene; R" is C₁₋₄ alkyl; R₂ is hydrogen or C₁₋₄ alkyl; R₁ is C₁₋₆ alkyl or hydroxy-C₁₋₆ alkyl; and n is 0.

In some embodiments, X is methylene; at least one of R" or R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl; R₁ is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or butyl; and n and m are 0.

In some embodiments, particularly embodiments of Formula V, X is methylene; at least one of R" or R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl; R₁ is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or butyl; and p and m are 0.

In some embodiments, particularly embodiments of Formula V, X is methylene; R" and R₂ are methyl; R₁ is 2-methylpropyl or 2-hydroxy-2-methylpropyl; and p and m are 0.

In some embodiments, particularly embodiments of Formula VI, X is methylene; R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl; R₁ is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or butyl; and R_{A2} and R_{B2} are each methyl.

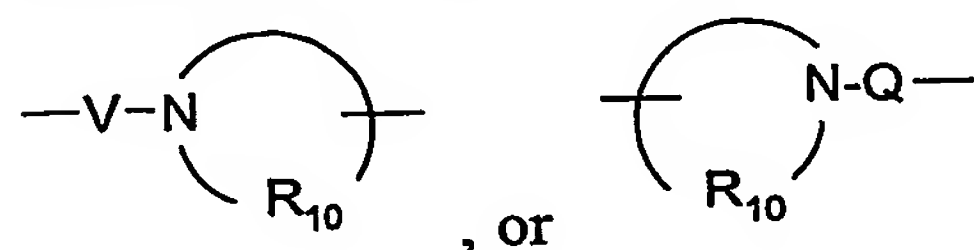
In some embodiments, particularly embodiments of Formula VI, X is methylene; R" and R₂ are methyl; R₁ is 2-methylpropyl or 2-hydroxy-2-methylpropyl; and R_{A2} and R_{B2} are each methyl.

In some embodiments, particularly embodiments of Formula IIIa, X is methylene; R₂ is methyl, ethyl, propyl, butyl, or 2-methylpropyl; R₁ is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or butyl; and n and m are 0.

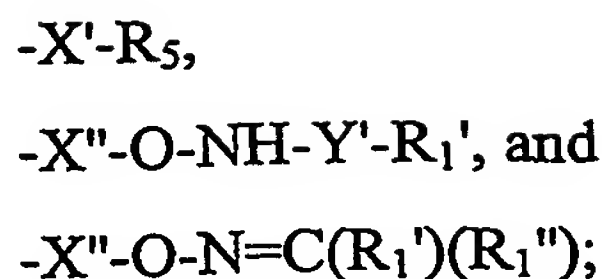
In some embodiments, X is methylene; R" and R₂ are methyl; R₁ is 2-methylpropyl or 2-hydroxy-2-methylpropyl; and n and m are 0.

In some embodiments, particularly embodiments of Formula IIIa, X is methylene; R" and R₂ are methyl; R₁ is 2-methylpropyl; and n and m are 0.

In some embodiments, R₁ is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R₄, and -X'-R₅; wherein X' is alkylene; Y is -N(R₈)-C(O)-, -N(R₈)-S(O)₂-, -N(R₈)-S(O)₂-N(R₈)-, -N(R₈)-C(O)-N(R₈)-, -N(R₈)-C(O)-N(R₈)-C(O)-,



; R₄ is hydrogen, alkyl, alkenyl, aryl, or heteroaryl, wherein alkyl and alkenyl are optionally substituted by aryl or aryloxy and wherein aryl is

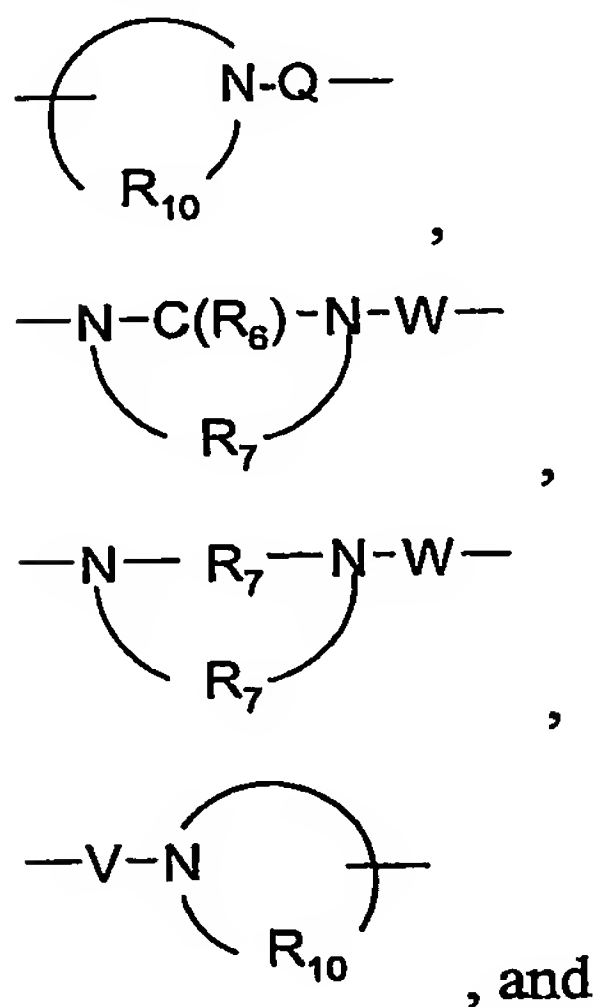
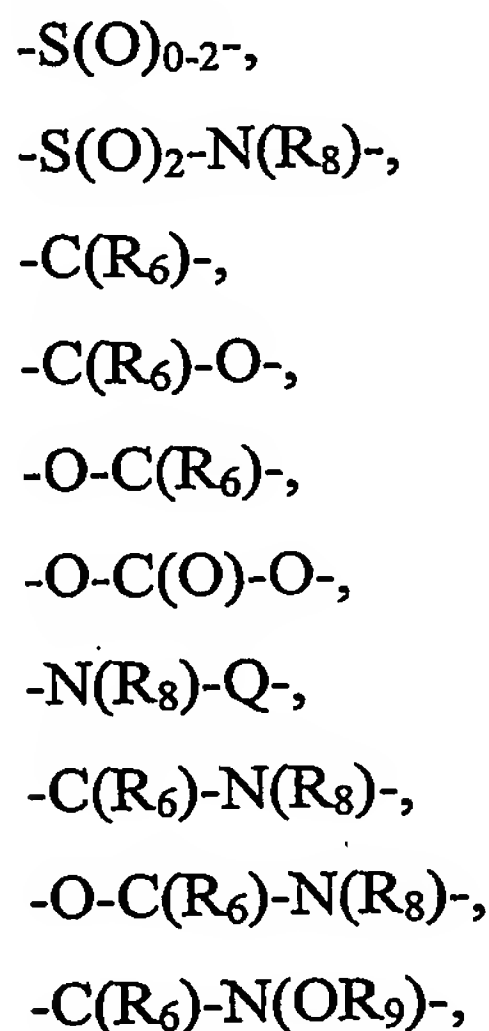


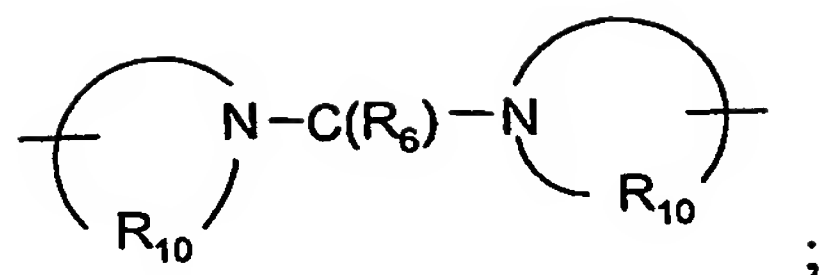
wherein:

5 X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-\text{CH}(\text{R}_{13})$ -alkylene- or $-\text{CH}(\text{R}_{13})$ -alkenylene-;

10 Y is selected from the group consisting of:





Y' is selected from the group consisting of:

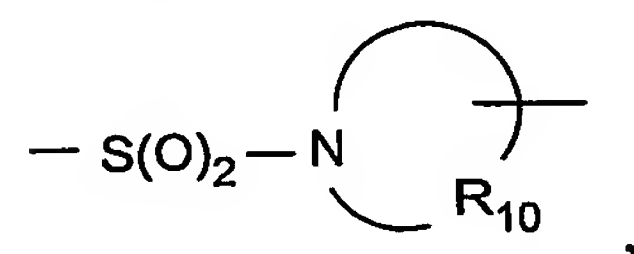
a bond,

-C(O)-,

-C(S)-,

-S(O)₂-,

-S(O)₂-N(R₈)-,



-C(O)-O-,

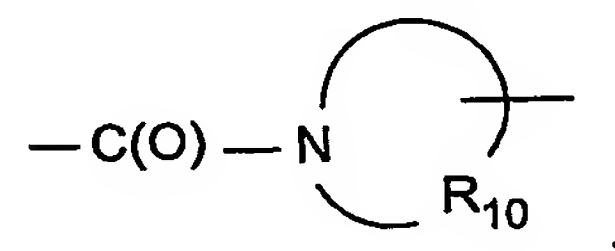
-C(O)-N(R₈)-,

-C(S)-N(R₈)-,

-C(O)-N(R₈)-S(O)₂-,

-C(O)-N(R₈)-C(O)-,

-C(S)-N(R₈)-C(O)-,



-C(O)-C(O)-,

-C(O)-C(O)-O-, and

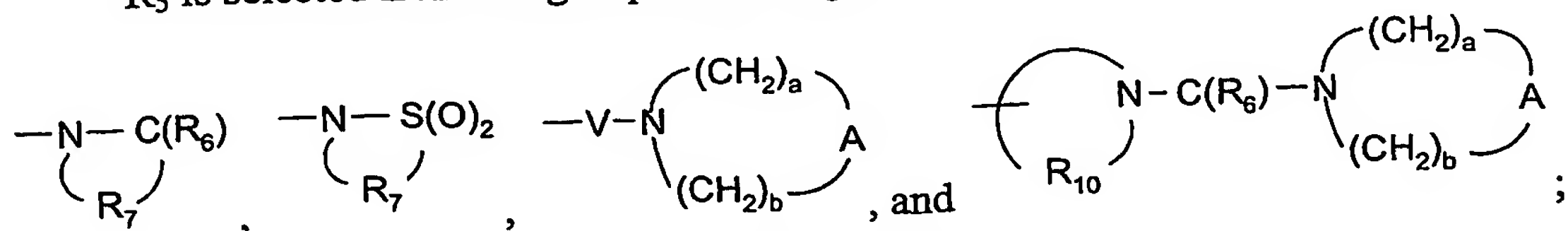
-C(=NH)-N(R₈)-;

R₁' and R₁" are the same as R₂ and R";

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy,

mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

5 R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C₂₋₇ alkylene;

R_8 is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl,

10 C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C₃₋₈ alkylene;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

15 A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and

-N(R₄)-

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and

20 -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

In some embodiments, particularly embodiments of Formula III, R^{'''} is R or R₃

25 when n is 1, R or one R and one R₃ when n is 2, or R when n is 3 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,
haloalkyl,
alkoxy,
alkylthio, and

-N(R₉)₂;

R₃ is selected from the group consisting of:

-Z-R₄,

-Z-X'-R₄,

-Z-X'-Y-R₄,

-Z-X'-Y-X'-Y-R₄, and

-Z-X'-R₅;

n is an integer from 0 to 4;

Z is a bond or -O-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)₀₋₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,

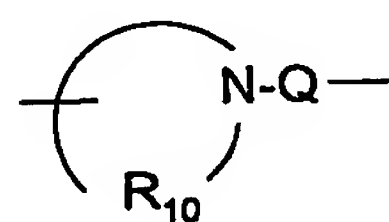
-O-C(O)-O-,

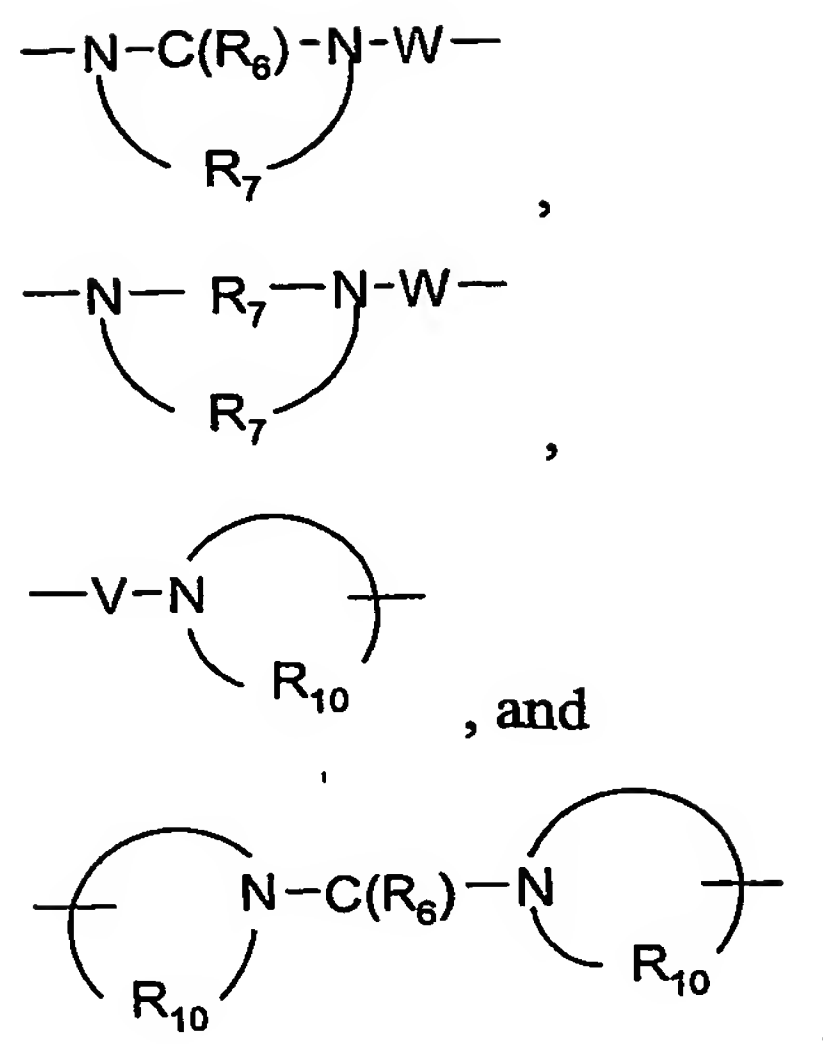
-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

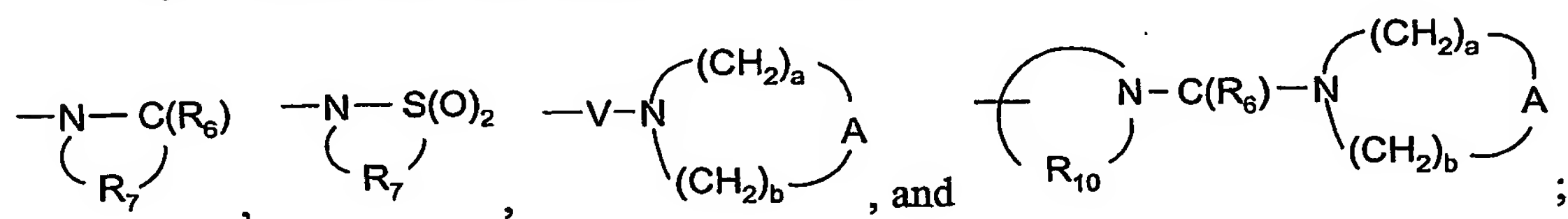
-C(R₆)-N(OR₉)-,





5 R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group
 10 consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
 15 oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

20 R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-\text{CH}_2-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_{0-2}-$, and $-\text{N}(\text{R}_4)-$;

Q is selected from the group consisting of a bond, $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)-\text{C}(\text{R}_6)-$, $-\text{S}(\text{O})_2-$, $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-\text{W}-$, $-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)-\text{O}-$, and $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$;

5 V is selected from the group consisting of $-\text{C}(\text{R}_6)-$, $-\text{O}-\text{C}(\text{R}_6)-$, $-\text{N}(\text{R}_8)-\text{C}(\text{R}_6)-$, and $-\text{S}(\text{O})_2-$;

W is selected from the group consisting of a bond, $-\text{C}(\text{O})-$, and $-\text{S}(\text{O})_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$.

10 In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is selected from the group consisting of alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, and heterocyclylalkylenyl are optionally substituted with one or more substituents defined above in the definition of R_2 .

15 In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is alkyl or substituted alkyl, and R'' is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 and R'' are independently alkyl.

20 In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is alkenyl or substituted alkenyl, and R'' is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and R'' is hydrogen.

25 In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is heteroaryl, heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and R'' is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and R'' is hydrogen.

30 In some embodiments, at least one of R'' or R_2 is alkyl or substituted alkyl, and at least one of R'' or R_2 is hydrogen.

In some embodiments, at least one of R" or R₂ is alkenyl or substituted alkenyl, and at least one of R" or R₂ is hydrogen.

In some embodiments, at least one of R" or R₂ is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and at least one of R" or R₂ is hydrogen.

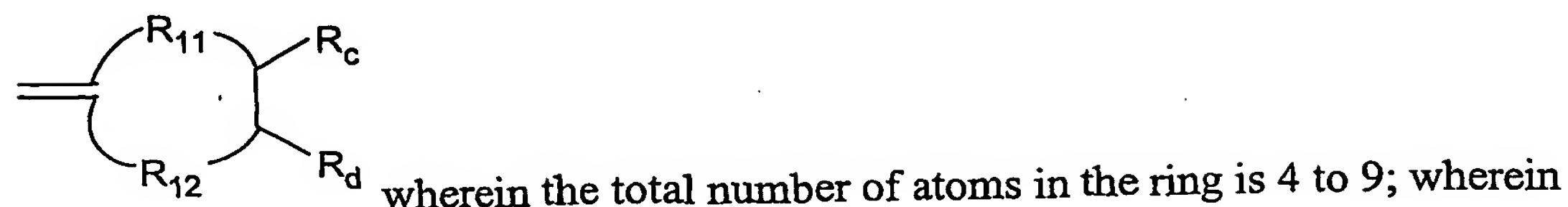
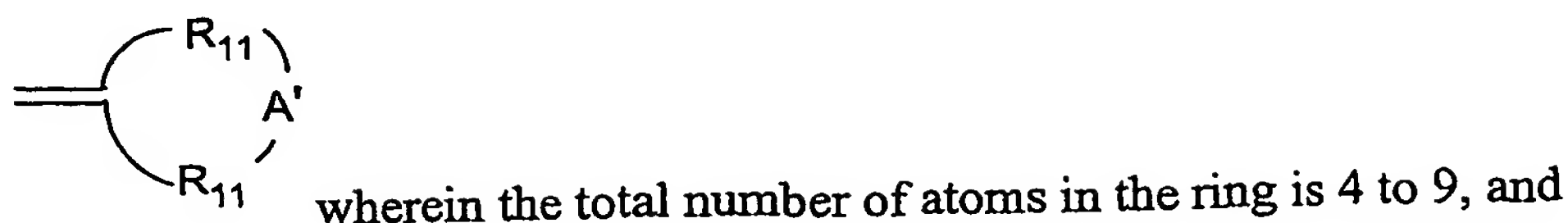
5 In some embodiments at least one of R" or R₂ is heteroaryl, heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and at least one of R" or R₂ is hydrogen.

10 In some embodiments, at least one of R" or R₂ is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and at least one of R" or R₂ is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R₂ is selected from the group consisting of methyl, ethyl, cyclopropyl, 2-(ethoxycarbonyl)cyclopropyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, cyclopentyl, 2-cyclopentylethyl, acetoxymethyl, (ethoxycarbonyl)methyl, furyl, furfuryl, cyclohexyl, tetrahydrofuranyl, 2-(methylthio)ethyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-trifluoromethylphenyl, phenylmethyl, phenoxymethyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethenyl, biphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-methylpyrrol-2-yl, 1-methylimidazol-2-yl, 1-methylimidazol-4-yl, 3-cyclohexen-1-yl, 3,4-dihydro-2*H*-pyran-2-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, 5-isoxazolyl, and quinolin-2-yl.

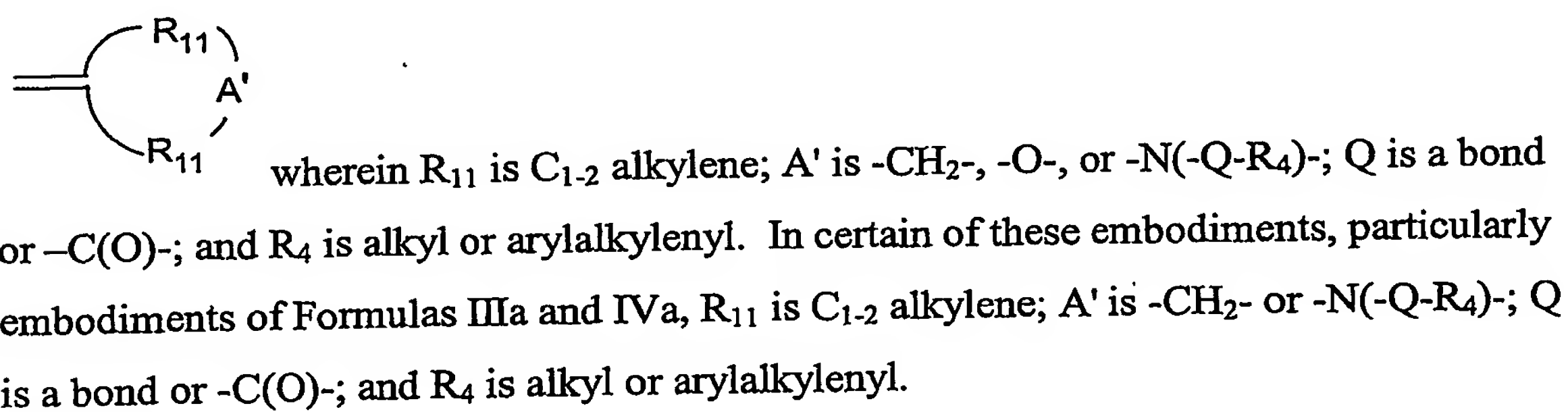
25 In some embodiments, R₂ and R" and/or R₁' and R₁" join together to form a ring system.

In some embodiments, the ring system formed by R₂ and R" and/or R₁' and R₁" is selected from the group consisting of:



R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom; R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom; R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms; and A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$.

In some embodiments, particularly for R_2 and R'' , the ring system is



In some embodiments, the ring system formed by R_2 and R'' and/or R_1' and R_1'' is selected from the group consisting of



wherein R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom; R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom; R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10

membered heteroaryl ring containing one to four hetero atoms; and A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-.

Preparation of the Compounds

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Compounds of the invention can be prepared according to Reaction Scheme I where R₁, R₂, R, R'', X, and n are as defined above, and Hal is chloro, bromo, or iodo. In step (1) of Reaction Scheme I, a quinoline-3,4-diamine of Formula X is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XI. Suitable equivalents to a carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired -X-Hal substituent in a compound of Formula XI. For example, Hal-X-CO₂H or Hal-X-C(O-alkyl)₃ will provide a compound with the desired -X-Hal substituent at the 2-position. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

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Alternatively, step (1) can be carried out by (i) reacting a compound of Formula X with an acyl halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula X in an inert solvent such as acetonitrile, pyridine or dichloromethane. The reaction can be carried out at ambient temperature. A catalyst such as pyridine hydrochloride can be included. Alternatively, the reaction can be carried out in the presence of triethylamine. In part (ii) the product of part (i) is heated in pyridine. The two steps can be combined into a single step when the reaction is run in pyridine or solvents such as dichloromethane or dichloroethane in the presence of triethylamine.

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Many compounds of Formula X are known and can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 4,929,624 (Gerster et al.), 5,268,376 (Gerster), 5,389,640 (Gerster et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.) 6,660,747 (Crooks et al.), 6,670,372

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(Charles et al.), 6,683,088 (Crooks et al.), 6,656,938 (Crooks et al.), and 6,664,264 (Dellaria et al.).

In step (2) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline of Formula XI is oxidized to provide an *N*-oxide of Formula XII using a conventional oxidizing agent that is capable of forming *N*-oxides. The reaction can be carried out by treating a solution of a compound of Formula XI in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (3) of Reaction Scheme I an *N*-oxide of Formula XII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XIII. The reaction is carried out in two parts. In part (i) a compound of Formula XII is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula XII in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

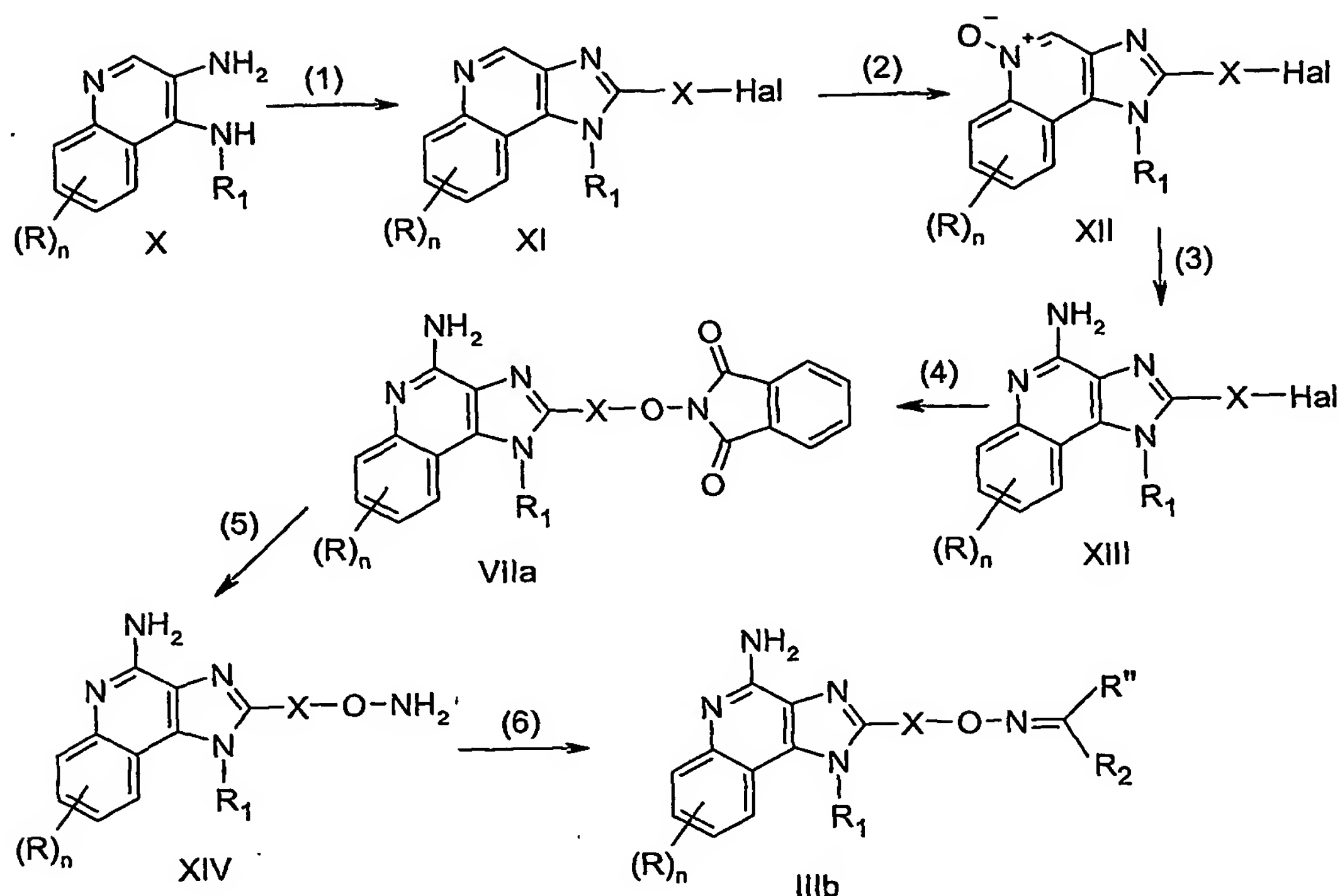
In step (4) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XIII is treated with *N*-hydroxyphthalimide to provide an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula VIIa. The reaction is conveniently carried out by adding a base, such as triethylamine, to a solution of *N*-hydroxyphthalimide in a suitable solvent such as *N,N*-dimethylformamide (DMF); and then adding the 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XIII in a suitable solvent (for example, DMF) to the resulting mixture. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (5) of Reaction Scheme I an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula VIIa is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV. Removal of the *N*-phthalimide protecting

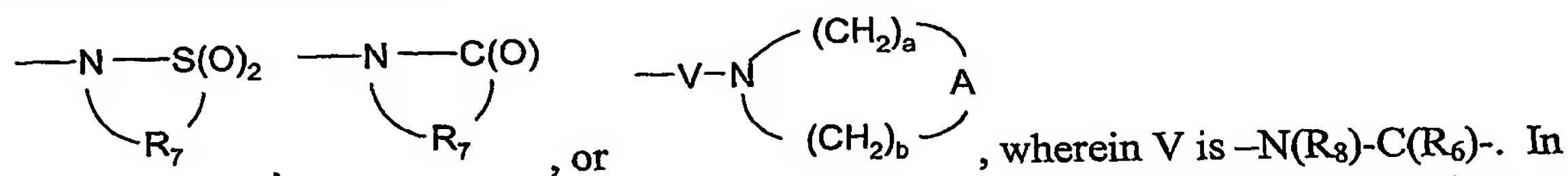
group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula VIIa in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV is reacted with an aldehyde or ketone of Formula $R_2C(O)R''$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula IIIb, which is a subgenus of Formulas I, II, III and IIIa. Numerous aldehydes and ketones of Formula $R_2C(O)R''$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of Formula $R_2C(O)R''$ to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIV in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods. Ketones such as acetone, tetrahydro-4*H*-pyran-4-one, 1-acetyl-4-piperidone, 1-benzyl-4-piperidone, and 1-methyl-4-piperidone can be used in step (6) to make preferred compounds of the invention.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R_2 , R_4 , R_8 , R , R'' , Q , X , X' , Hal, and n are as defined above, Boc is *tert*-butoxycarbonyl, and R_{5a} is



step (1) of Reaction Scheme II a 1H-imidazo[4,5-c]quinolin-1-yl *tert*-butylcarbamate of Formula XV is treated with *N*-hydroxyphthalimide to provide an *N*-phthalimide-protected 1H-imidazo[4,5-c]quinolin-2-yl hydroxylamine of Formula XVI, which is a subgenus of Formulas VII and VIIa. The reaction is conveniently carried out by adding a base, such as triethylamine, to a solution of *N*-hydroxyphthalimide in a suitable solvent such as DMF; and then adding the 1H-imidazo[4,5-c]quinolin-1-yl *tert*-butylcarbamate of Formula XV in a suitable solvent (for example, DMF) to the resulting mixture. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Compounds of Formula XV can be readily prepared using known synthetic routes; see for example, U.S. Patent No. 6,451,485

(Crooks et al.), and 6,660,747 (Crooks et al.) to prepare a quinoline-3,4-diamine that can be treated according to steps (1) to (3) of Reaction Scheme I.

In step (2) of Reaction Scheme II an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XVI is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XVII. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XVI in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

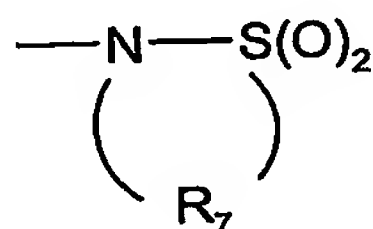
In step (3) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XVII is reacted with an aldehyde or ketone of Formula $R_2C(O)R''$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVIII, which is a subgenus of Formulas I, II, III and IIIa. Numerous aldehydes and ketones of Formula $R_2C(O)R''$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of Formula $R_2C(O)R''$ to a solution of the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVII in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods. Ketones such as acetone, tetrahydro-4*H*-pyran-4-one, 1-acetyl-4-piperidone, 1-benzyl-4-piperidone, and 1-methyl-4-piperidone can be used in this step to make preferred compounds of the invention.

In step (4) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVIII is deprotected to provide an amino group at the 1-position of a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XIX. The reaction can be conveniently carried out by dissolving a compound of Formula XVIII in a mixture of trifluoroacetic acid and a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof, including the trifluoroacetate salt, can be isolated using conventional methods.

In steps (5) and (5a) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XIX is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of

Formulas XX or XXI, which are subgenera of Formulas I, II, III, and IIIa, using conventional methods. For example, sulfonamides of Formula XX can be prepared by reacting a compound of Formula XIX with a sulfonyl chloride of Formula $R_4S(O)_2Cl$. The reaction can be carried out at ambient temperature in an inert solvent such as chloroform or dichloromethane by adding the sulfonyl chloride to a compound of Formula XIX in the presence of a base such as *N,N*-diisopropylethylamine, triethylamine, or pyridine. Sulfamides of Formula XX can be prepared by reacting a compound of Formula XIX with a sulfamoyl chloride of Formula $R_4(R_8)NS(O)_2Cl$ or with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of Formula $HN(R_8)R_4$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Some sulfamoyl chlorides of Formula $R_4(R_8)NS(O)_2Cl$ and many sulfonyl chlorides of Formula $R_4S(O)_2Cl$ and amines of Formula $HN(R_8)R_4$ are commercially available; others can be prepared using known synthetic methods.

In another example shown in step (5a) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XIX is reacted with a chloroalkanesulfonyl chloride of Formula Cl-R₇-S(O)₂Cl to provide a compound of Formula XXI, wherein R_{5a} is a ring having the structure

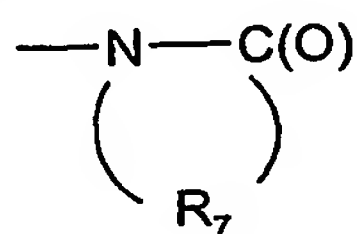


The reaction is preferably carried out by adding the chloroalkanesulfonyl chloride to a solution of a compound of Formula XIX in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine. The intermediate chloroalkanesulfonamide may optionally be isolated before treatment with a stronger base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at ambient temperature. If the intermediate chloroalkanesulfonamide is isolated, the reaction with DBU can be carried out in a suitable solvent such as DMF. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Amides of Formulas XX and XXI can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XIX using conventional methods. For example, a compound of Formula XIX can be reacted with an acid chloride of Formula $R_4C(O)Cl$ to

provide a compound of Formula XX. The reaction can be carried out by adding the acid chloride to a solution of a compound of Formula XIX in a suitable solvent such as chloroform, optionally in the presence of a base such as *N,N*-diisopropylethylamine, triethylamine, or pyridine, at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

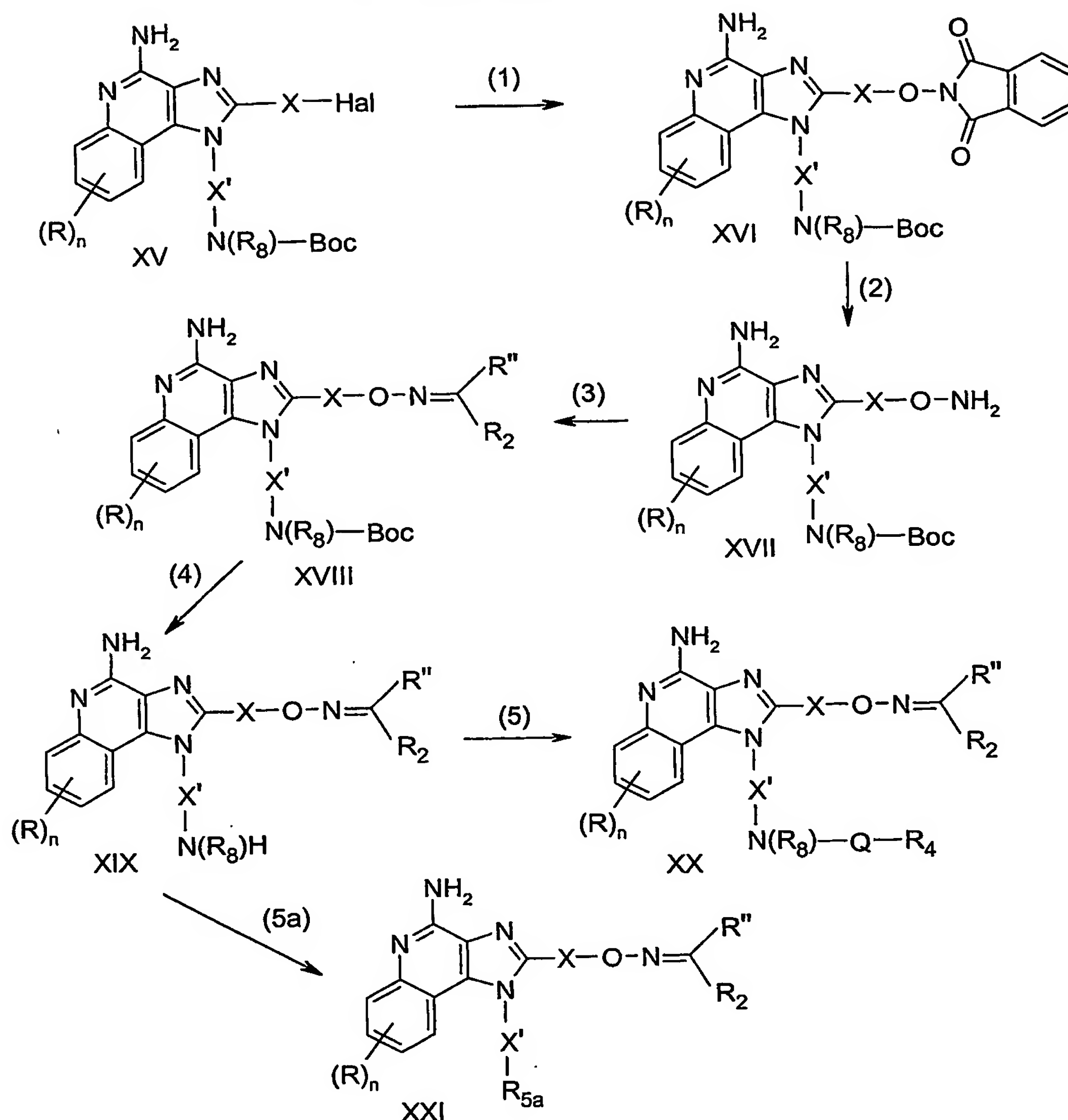
In another example shown in step (5a), a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XIX is reacted with a chloroalkanoyl chloride compound of Formula Cl-R₇-C(O)Cl to provide a compound of Formula XXI, wherein R_{5a} is a ring having the structure



The reaction is preferably carried out by adding the chloroalkanoyl chloride compound to a compound of Formula XIX in a suitable solvent such as dichloromethane in the presence of a base such as *N,N*-diisopropylethylamine. The intermediate chloroalkanamide may optionally be isolated before treatment with a stronger base such as DBU at ambient temperature. If the intermediate chloroalkanamide is isolated, the reaction with DBU can be carried out in a suitable solvent such as DMF. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas and thioureas of Formulas XX and XXI can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl oximes of Formula XIX using conventional methods. For example, a compound of Formula XIX can be reacted with an isocyanate of Formula $R_4N=C=O$. The reaction can be carried out by adding the isocyanate to a solution of a compound of Formula XIX in a suitable solvent such as chloroform, optionally in the presence of a base such as *N,N*-diisopropylethylamine, or triethylamine, at ambient temperature. Alternatively, a compound of Formula XIX can be reacted with a thioisocyanate of Formula $R_4N=C=S$, a sulfonyl isocyanate of Formula $R_4S(O)_2N=C=O$ or a carbamoyl chloride of Formula $R_4N(R_8)C(O)Cl$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



5 Compounds of the invention can be prepared according to Reaction Scheme III where R_2 , R'' , and n are as defined above; X_c is C_{1-10} alkylene; P is a removable protecting group, such as an alkanoyloxy group (e.g., acetoxy) or an aroyloxy group (e.g., benzoyloxy); R_B is selected from the group consisting of hydroxy, alkyl, alkoxy, $-N(R_9)_2$; and R_{1c} is a subset of R_1 as defined above, which does not include those groups that one skilled in the art would recognize as being susceptible to reduction in step (5). These groups include, for example, alkenyl, alkynyl, and aryl groups, and groups bearing nitro and $-S-$ substituents.

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In step (1) of Reaction Scheme III a quinoline-3,4-diamine of Formula Xa is reacted with a carboxylic acid of the formula, HO-X-CO₂H, with a trialkyl orthoester of the formula, HO-X-C(O-C₁₋₄ alkyl)₃, or with a combination thereof (wherein "alkyl" is a straight or branched chain) to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl alcohol of Formula XXII. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included. Compounds of Formula Xa are a subset of compounds of Formula X, which are shown in Reaction Scheme I.

In step (2) of Reaction Scheme III, the hydroxyl group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXII is protected with a removable protecting group such as an alkanoyloxy group (e.g., acetoxy) or aroyloxy group (e.g., benzoyloxy) to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. Suitable protecting groups and reactions for their placement and removal are well known to those skilled in the art. See, for example, U.S. Patent No. 4,689,338 (Gerster), Examples 115 and 120 and 5,389,640 (Gerster et al.), Examples 2 and 3.

For some embodiments, it is possible to combine steps (1) and (2) when an acid chloride of the Formula PO-X-CO₂Cl is used under the conditions of step (1). Some acid chlorides of this type, for example, acetoxyacetyl chloride, are commercially available.

In step (3) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII is oxidized to provide an *N*-oxide of Formula XXIV using a conventional oxidizing agent that is capable of forming *N*-oxides. The reaction can be carried out by treating a solution of a compound of Formula XXIII in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (4) of Reaction Scheme III, an *N*-oxide of Formula XXIV is aminated and the protecting group removed to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXV. The amination reaction is carried out in two parts. In part (i) a compound of Formula XXIV is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium

bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula XXIV in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The protecting group is removed by using conventional methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (5) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXV is reduced to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXVI. The reaction can be conveniently carried out by suspending or dissolving a compound of Formula XXV in ethanol, adding a catalytic amount of rhodium on carbon, and hydrogenating. Alternatively, the reaction can be carried out by suspending or dissolving a compound of Formula XXV in trifluoroacetic acid, and adding platinum(IV) oxide, and hydrogenating. The reaction can be carried out in a Parr apparatus. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme III a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXVI is treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula VIIc. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of a compound of Formula XXVI in a suitable solvent such as tetrahydrofuran or DMF, and then slowly adding diethyl azodicarboxylate or diisopropyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60 °C. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

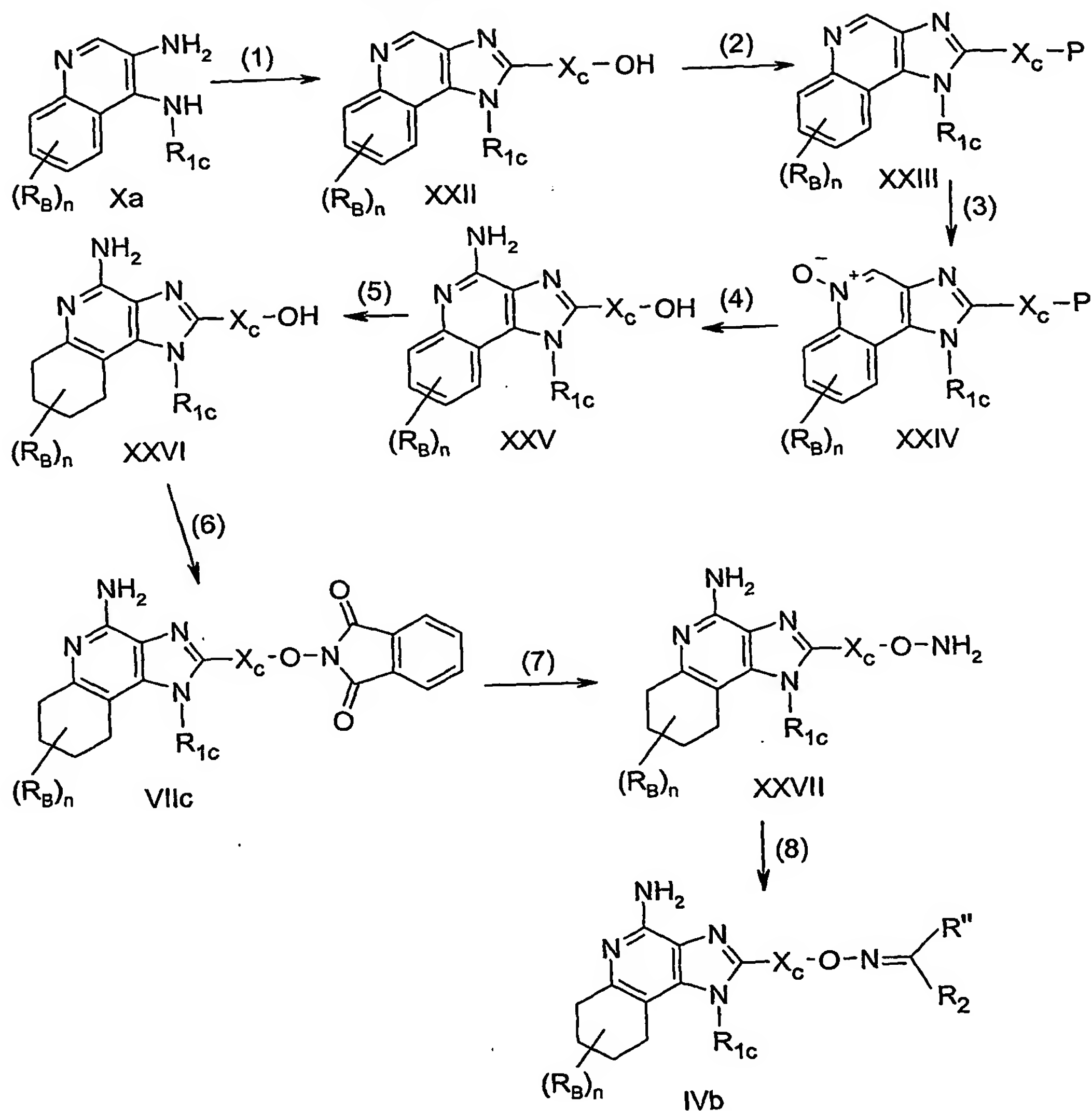
Alternatively, step (6) may be carried out in two parts by (i) converting the hydroxy group in a compound of Formula XXVI to a leaving group and (ii) displacing the leaving group with *N*-hydroxyphthalimide in the presence of a base. Part (i) of step (6) is conveniently carried out by treating the hydroxy-substituted 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXVI with thionyl chloride in a suitable solvent such as 1,2-dichloroethane. The reaction may be carried out at ambient temperature, and the product may be isolated by conventional methods. Part (ii) of step (6)

can be carried out under the conditions described in step (4) of Reaction Scheme I, and the product of Formula VIIc or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

5 In step (7) of Reaction Scheme III an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula VIIc is converted to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVII. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula VIIc in a suitable solvent such as ethanol. The reaction
10 can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (8) of Reaction Scheme III a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVII is reacted with an aldehyde or ketone of Formula $R_2C(O)R''$ to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of
15 Formula IVb as in step (3) of Reaction Scheme II. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

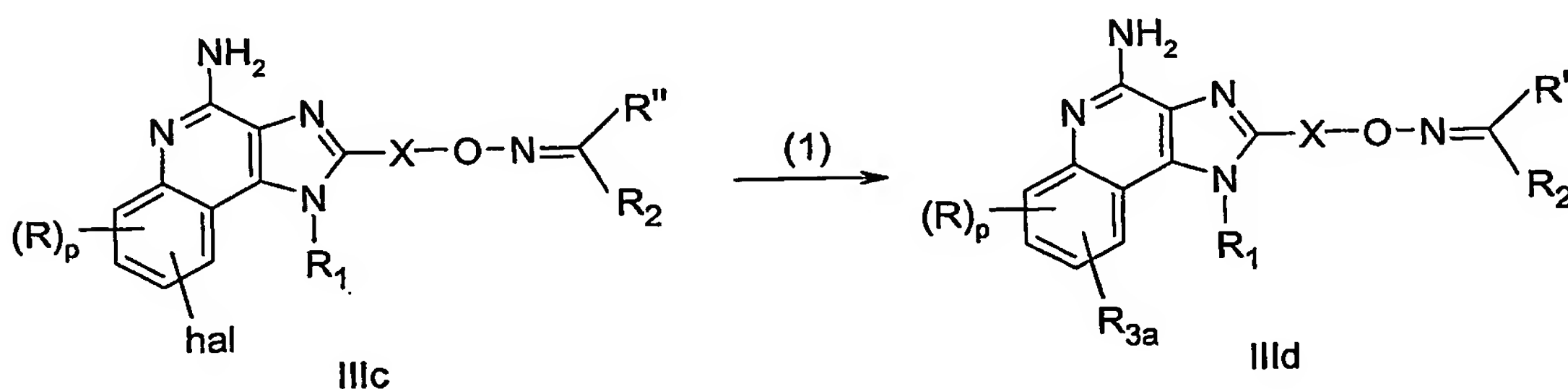
Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV where R₁, R₂, R, R'', and X are as defined above, hal is bromo or iodo, p is 0 to 3, and R_{3a} is -R_{4b}, -X'_a-R₄, -X'_b-Y-R₄, or -X'_b-R₅; where X'_a is alkenylene; X'_b is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R₄ above; and R₄, R₅, and Y are as defined above. In step (1) of Reaction Scheme IV a halogen substituted 1H-imidazo[4,5-c]quinolin-2-yl oxime of Formula IIIc is coupled with a boronic acid of the formula R_{3a}-B(OH)₂ (or the corresponding anhydride or esters, R_{3a}-B(O-alkyl)₂, thereof) using Suzuki coupling conditions to provide a 1H-

imidazo[4,5-*c*]quinolin-2-yl oxime of Formula IIIc. A compound of Formula IIIc is combined with a boronic acid of the formula $R_{3a}\text{-B(OH)}_2$ or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine and a base such as aqueous sodium carbonate in a suitable solvent such as *n*-propanol or *n*-propanol and water. The reaction can be carried out at an elevated temperature (e.g., 80 °C-100 °C). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Halogen substituted 1*H*-imidazo[4,5-*c*]quinolin-2-yl oximes of Formula IIIc can be prepared as described above in steps (1)-(6) of Reaction Scheme I or steps (1) – (5) or (5a) or Reaction Scheme II, wherein one of the R groups is hal. Numerous boronic acids of Formula $R_{3a}\text{-B(OH)}_2$, anhydrides thereof, and boronic acid esters of Formula $R_{3a}\text{-B(O-alkyl)}_2$ are commercially available; others can be readily prepared using known synthetic methods.

Reaction Scheme IV



Compounds of the invention can be prepared according to Reaction Scheme V where R_1 , R_2 , R'' , R , X , and Hal , are as defined above; E is carbon (imidazoquinoline ring) or nitrogen (imidazonaphthyridine ring); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring) with the proviso that when m is 1, then n is 0 or 1; and D is $-\text{Br}$, $-\text{I}$, or $-\text{OCH}_2\text{Ph}$; wherein Ph is phenyl. In step (1) of Reaction Scheme V, an aniline or aminopyridine of Formula XXVIII is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XXIX. The reaction is conveniently carried out by adding a solution of an aniline or aminopyridine of Formula XXVIII to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature. The product can be isolated using conventional

methods. Many anilines and aminopyridines of Formula XXVIII are commercially available; others can be prepared by known synthetic methods. For example, benzyloxypyridines of Formula XXVIII can be prepared using the method of Holladay et al., *Biorg. Med. Chem. Lett.*, 8, pp. 2797-2802, (1998).

5. In step (2) of Reaction Scheme V, an imine of Formula XXIX undergoes thermolysis and cyclization to provide a compound of Formula XXX. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature of 200 °C to 250 °C. The product can be isolated using conventional methods. Isomers of the compound of Formula XXVIII or Formula XXX, wherein E is
10 nitrogen, can also be synthesized and can be used to prepare compounds of the invention.

In step (3) of Reaction Scheme V, a compound of Formula XXX is nitrated under conventional nitration conditions to provide a compound of Formula XXXI. The reaction is conveniently carried out by adding nitric acid to the compound of Formula XXX in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature.
15 The product can be isolated using conventional methods.

In step (4) of Reaction Scheme V, a 3-nitro[1,5]naphthyridin-4-ol or 3-nitroquinolin-4-ol of Formula XXXI is chlorinated using conventional chlorination chemistry to provide a 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of
20 Formula XXXII. The reaction is conveniently carried out by treating the compound of Formula XXXI with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at ambient temperature or at an elevated temperature such as 100 °C, and the product can be isolated using conventional methods.

The 4-chloro-3-nitro[1,5]naphthyridine of Formula XXXII wherein m and n are both 0 is known and can be readily prepared using a known synthetic route; see for
25 example, U.S. Patent No. 6,194,425 (Gerster et al.).

In step (5) of Reaction Scheme V, a 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XXXII is treated with an amine of Formula R_1-NH_2 to provide a compound of Formula XXXIII. Several amines of Formula R_1-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction
30 is conveniently carried out by adding the amine of Formula R_1-NH_2 to a solution of the 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XXXII in a

suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as, for example, 0 °C. The reaction product can be isolated using conventional methods.

5 In step (6) of Reaction Scheme V, a compound of Formula XXXIII is reduced to provide a diamine of Formula XXXIV. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as palladium on carbon or platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, acetonitrile, or ethyl acetate. For compounds of the
10 Formula XXXIII wherein m is 1 and D is -OCH₂Ph, the preferred catalyst is platinum on carbon. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

Alternatively, the reduction in step (6) can be carried out using nickel boride, prepared *in situ* from sodium borohydride and nickel(II) chloride. The reduction is
15 conveniently carried out by adding a solution of a compound of Formula XXXIII in a suitable solvent or solvent mixture such as dichloromethane/methanol to a mixture of excess sodium borohydride and catalytic nickel(II) chloride in methanol. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

20 In step (7) of Reaction Scheme V, a diamine of Formula XXXIV, is reacted with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXV. The carboxylic acid or equivalent is selected such that it will provide the desired -X-Hal substituent in a compound of Formula XXXV and the reaction can be carried out as described in step (1) of Reaction Scheme I. When an
25 acid chloride, for example chloroacetyl chloride, is used as the carboxylic acid equivalent, the reaction can be carried out in two steps. Part (i) of step (7) is conveniently carried out by adding the acid chloride to a solution of a diamine of Formula XXXIV in a suitable solvent such as dichloromethane, chloroform, or acetonitrile. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction
30 can be carried out at ambient temperature. The amide product or the salt thereof can be isolated and optionally purified using conventional techniques. Part (ii) of step (7)

involves heating the amide prepared in part (i) in the presence of base to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXV. The reaction is conveniently carried out in a suitable solvent such as ethanol in the presence of a base such as aqueous sodium hydroxide, aqueous potassium carbonate, or triethylamine at elevated temperature. In some instances, the product of Formula XXXV may be obtained directly from Part (i). Alternatively, a diamine of Formula XXXIV can be treated with ethyl chloroacetimidate hydrochloride as the carboxylic acid equivalent to provide a compound wherein X is methylene. The reaction is carried out in a suitable solvent such as chloroform at ambient temperature and the product of Formula XXXV can be isolated using conventional methods. Ethyl chloroacetimidate hydrochloride is a known compound that can be prepared according to the literature procedure: Stillings, M. R. et al., *J. Med. Chem.*, 29, pp. 2280-2284 (1986).

In steps (8) – (10) of Reaction Scheme V, a chloro-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXV can be converted into phthalimide-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXVIII using the chemistry described in steps (2) – (4) of Reaction Scheme I. Steps (8) and (9) can alternatively be combined and carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXXV in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride without isolating the *N*-oxide of Formula XXXVI. Compounds of Formula XXXVI, XXXVII, and XXXVIII or their pharmaceutically acceptable salts can be isolated using conventional methods.

In steps (11) and (12) of Reaction Scheme V, a phthalimide-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXVIII is converted to a hydroxylamine-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXIX which is condensed with an aldehyde or ketone to form an oxime of Formula XL, sequentially using the chemistry described in steps (5) and (6) of Reaction Scheme I. Compounds of Formula XXXIX and XL or their pharmaceutically acceptable salts can be isolated using conventional methods.

For some embodiments, compounds shown in Reaction Scheme V can be further elaborated using conventional synthetic methods. For example, an amine of Formula R_1-NH_2 , used in step (5) of Reaction Scheme V, may contain a protected functional group, such as a *tert*-butoxycarbonyl-protected amino group. The protecting group may be removed after step (12) of Reaction Scheme V to reveal an amine on the R_1 group. An amino group introduced in this manner may be further functionalized using the chemistry described in steps (5) and (5a) of Reaction Scheme II to provide compounds of the Formula XL in which R_1 is $-X'-N(R_8)-Q-R_4$ or $-X'-R_{5a}$. Alternatively, the protecting group may be removed after step (7) in Reaction Scheme V and the resulting amino group may be functionalized as described above before step (8). The resulting compound of Formula XXXV can be subjected to steps (8) - (12) of Reaction Scheme V to provide a compound of Formula XL wherein R_1 is $-X'-N(R_8)-Q-R_4$ or $-X'-R_{5a}$.

Alternatively, the amine of Formula R_1-NH_2 used in step (5) of Reaction Scheme V may contain an appropriately-protected hydroxyl group, for example, a *tert*-butyldimethylsilyl-protected hydroxyl group. The protecting group may be removed after step (12) in Reaction Scheme V to provide an alcohol on the R_1 group. An alcohol introduced in this manner into a compound of Formula XL may be converted into a hydroxylamine upon treatment with *N*-hydroxyphthalimide using the Mitsunobu reaction conditions described in step (6) of Reaction Scheme III, followed by deprotection of the resulting phthalimide-protected hydroxylamine with hydrazine in ethanol. A hydroxylamine on the R_1 group can undergo reaction with a ketone or aldehyde of Formula $R_1'C(O)R_1''$ to form an oxime using the reaction conditions described in step (6) of Reaction Scheme I to yield a compound of Formula XL in which R_1 is $-X''-O-N=C(R_1')(R_1'')$ where X'' , R_1' , and R_1'' are as defined above.

A hydroxylamine on the R_1 group of a compound of Formula XL, prepared as described above, can also be further functionalized to a compound of the Formula XL in which R_1 is $-X''-O-NR_{1a}-Y'-R_{1b}$ wherein Y' is $-C(O)-$, $-S(O)_2-$, $-C(O)-N(R_8)-$, $-C(S)-N(R_8)-$, $-C(O)-N(R_8)-S(O)_2-$, $-C(O)-N(R_8)-C(O)-$, $-S(O)_2-N(R_8)-$; R_{1a} is hydrogen, and R_{1b} is as defined above using, respectively, an acid chloride, a sulfonyl chloride or a sulfonic anhydride; an isocyanate; an acyl isocyanate, an isothiocyanate, a sulfonyl isocyanate, a carbamoyl chloride, or a sulfamoyl chloride. The reaction can be carried out

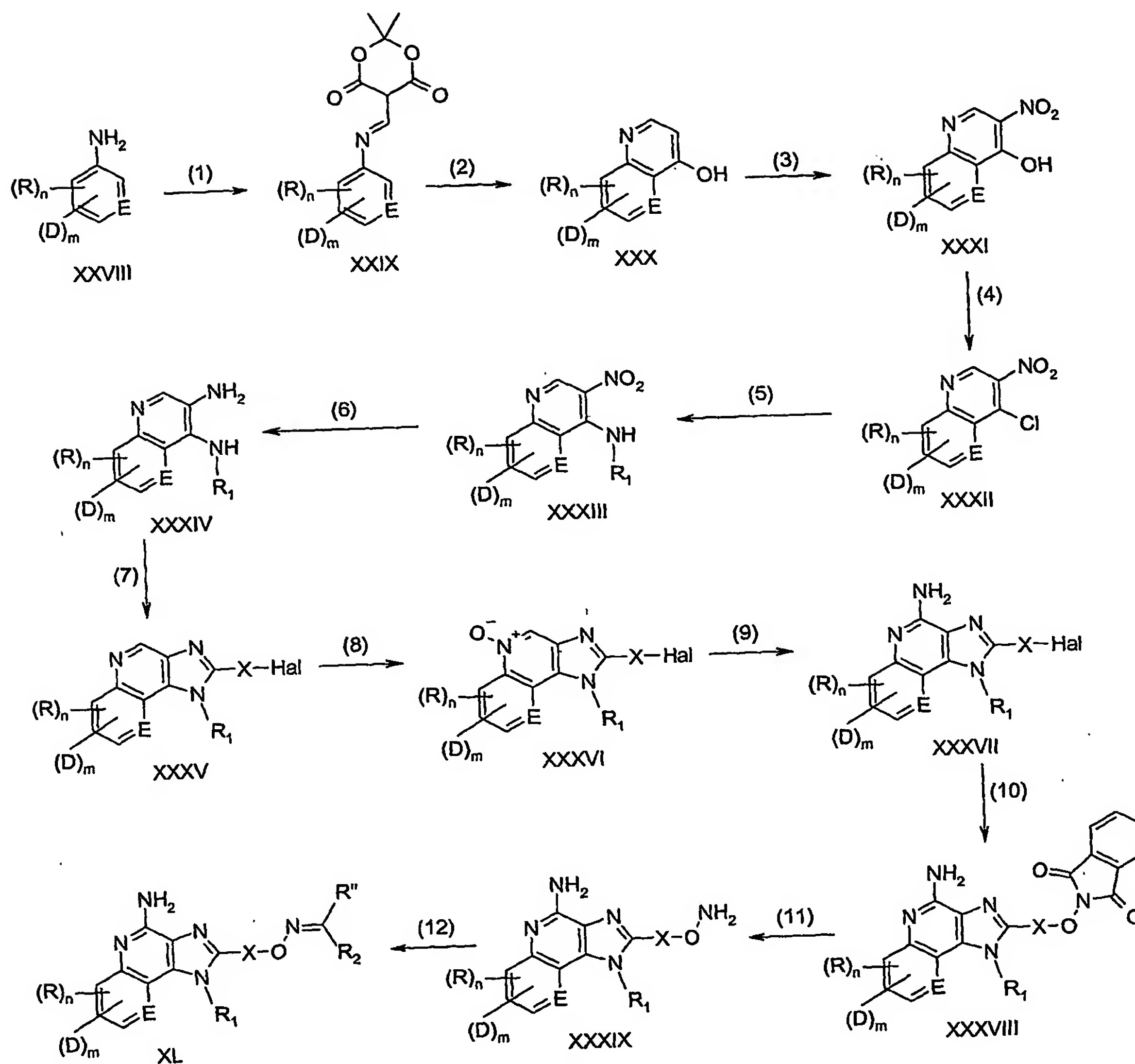
using the conditions described in step (5) of Reaction Scheme II. A large number of the reagents listed above are commercially available; others can be readily prepared using known synthetic methods.

A compound of Formula XL in which R_1 is $-X''-O-NR_{1a}-Y'-R_{1b}$ wherein Y' is a bond, $-C(O)-$, $-C(S)-$, $-S(O)_2-$, or $-C(O)-C(O)-$; R_{1b} is defined above, and R_{1a} is hydrogen, can be derivatized further upon treatment with an alkylating agent that is generated in situ from an alcohol of Formula $R_{1a}-OH$ under Mitsunobu reaction conditions (described in step (6) of Reaction Scheme III) or an alkylating agent of Formula $R_{1a}-Br$ or $R_{1a}-I$ in the presence of a base such as cesium carbonate in a suitable solvent such as DMF. The later reaction may be carried out at ambient temperature for reactive alkylating agents such as, for example, methyl iodide, benzyl bromide, and substituted benzyl bromides, or at an elevated temperature. Optionally, catalytic tetrabutylammonium hydrogensulfate can be added. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods. One skilled in the art would recognize that the reactions described for the alkylation step would probably not be successful for R_{1a} groups that are difficult to introduce via bimolecular nucleophilic substitution reactions. These groups include, for example, sterically hindered alkyl groups.

A compound of Formula XL in which R_1 is $-X''-O-NR_{1a}-Y'-R_{1b}$, where R_{1a} and R_{1b} together with the nitrogen atom and Y' group to which they are bonded join together to

form a ring of Formula $\begin{array}{c} \text{—N—C(O)} \\ | \\ \text{(R}_7\text{)} \end{array}$ or $\begin{array}{c} \text{—N—S(O)}_2 \\ | \\ \text{(R}_7\text{)} \end{array}$, can be prepared in a two-step procedure from a compound of Formula XL in which R₁ is -X''-O-NH₂, using the methods described in step 5a of Reaction Scheme I. Alternatively, a reagent of the Formula P-O-R₇C(O)Cl, wherein P is a protecting group, may react with a compound of Formula XL in which R₁ is -X''-O-NH₂ to generate an isolable intermediate that can then be deprotected to yield a hydroxyalkanamide. The isolable hydroxyalkanamide is cyclized under Mitsunobu conditions, described in step (6) of Reaction Scheme III. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme V



Compounds of the invention can be prepared according to Reaction Scheme VI, wherein D, E, R, R₁, R₂, R'', and hal are as defined above, m is 1, n is 0 or 1, and R_{3b} and R_{3c} are as defined below. In Reaction Scheme VI, when D is -Br or -I, step (1) is used to convert a hydroxylamine-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XXXIX to an oxime-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XLI, a subgenus of Formulas I and II, as in step (12) of Reaction Scheme V.

In step (2) of Reaction Scheme VI, a bromo- or iodo-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XLI can undergo known palladium-catalyzed coupling reactions such as the Suzuki coupling and the Heck reaction. For example, a bromo or iodo-substituted compound of Formula XLI
5 undergoes Suzuki coupling with a boronic acid of Formula $R_{3a}\text{-B(OH)}_2$, an anhydride thereof, or a boronic acid ester of Formula $R_{3a}\text{-B(O-alkyl)}_2$, wherein R_{3a} is as defined above, according to the method described in Reaction Scheme IV. The product of Formula XLII, a subgenus of Formulas I and II wherein R_{3b} is the same as R_{3a} , or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

10 The Heck reaction can also be used in step (2) of Reaction Scheme VI to provide compounds of Formula XLII, wherein R_{3b} is $\text{-X}'_a\text{-R}_{4b}$ and $\text{-X}'_a\text{-Y-R}_4$, wherein X'_a , Y, R_{4b} , and R_4 are as defined above. The Heck reaction is carried out by coupling a compound of Formula XLI with a compound of the Formula $\text{H}_2\text{C=C(H)-R}_{4b}$ or $\text{H}_2\text{C=C(H)-Y-R}_4$. Several of these vinyl-substituted compounds are commercially available; others can be
15 prepared by known methods. The reaction is conveniently carried out by combining the compound of Formula XLI and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100 °C -120 °C under an inert atmosphere.
20 The product of Formula XLII or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula XLII, wherein R_{3b} is $\text{-X}'_c\text{-R}_4$, X'_c is alkynylene, and R_4 is as defined above, can also be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a
25 compound of Formula XLI with a compound of the Formula $(\text{alkyl})_3\text{Sn-C}\equiv\text{C-R}_4$, $(\text{alkyl})_3\text{Si-C}\equiv\text{C-R}_4$, or $\text{H-C}\equiv\text{C-R}_4$.

Compounds of Formula XLII prepared as described above by palladium-mediated coupling reactions, wherein R_{3b} is $\text{-X}'_a\text{-R}_4$, $\text{-X}'_a\text{-Y-R}_4$, $\text{-X}'_{b2}\text{-Y-R}_4$, $\text{-X}'_{b2}\text{-R}_5$, or $\text{-X}'_c\text{-R}_4$, where X'_{b2} is alkenylene interrupted or terminated by arylene or heteroarylene, and X'_a ,
30 X'_c , Y, R_4 , and R_5 are as defined above, can undergo reduction of the alkenylene or alkynylene group present to provide compounds of Formula XL wherein R_{3b} is $\text{-X}'_d\text{-R}_4$,

-X'_d-Y-R₄, -X'_e-Y-R₄, or -X'_e-R₅, where X'_d is alkylene; X'_e is alkylene interrupted or terminated by arylene or heteroarylene; and R₄, R₅, and Y are as defined above. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

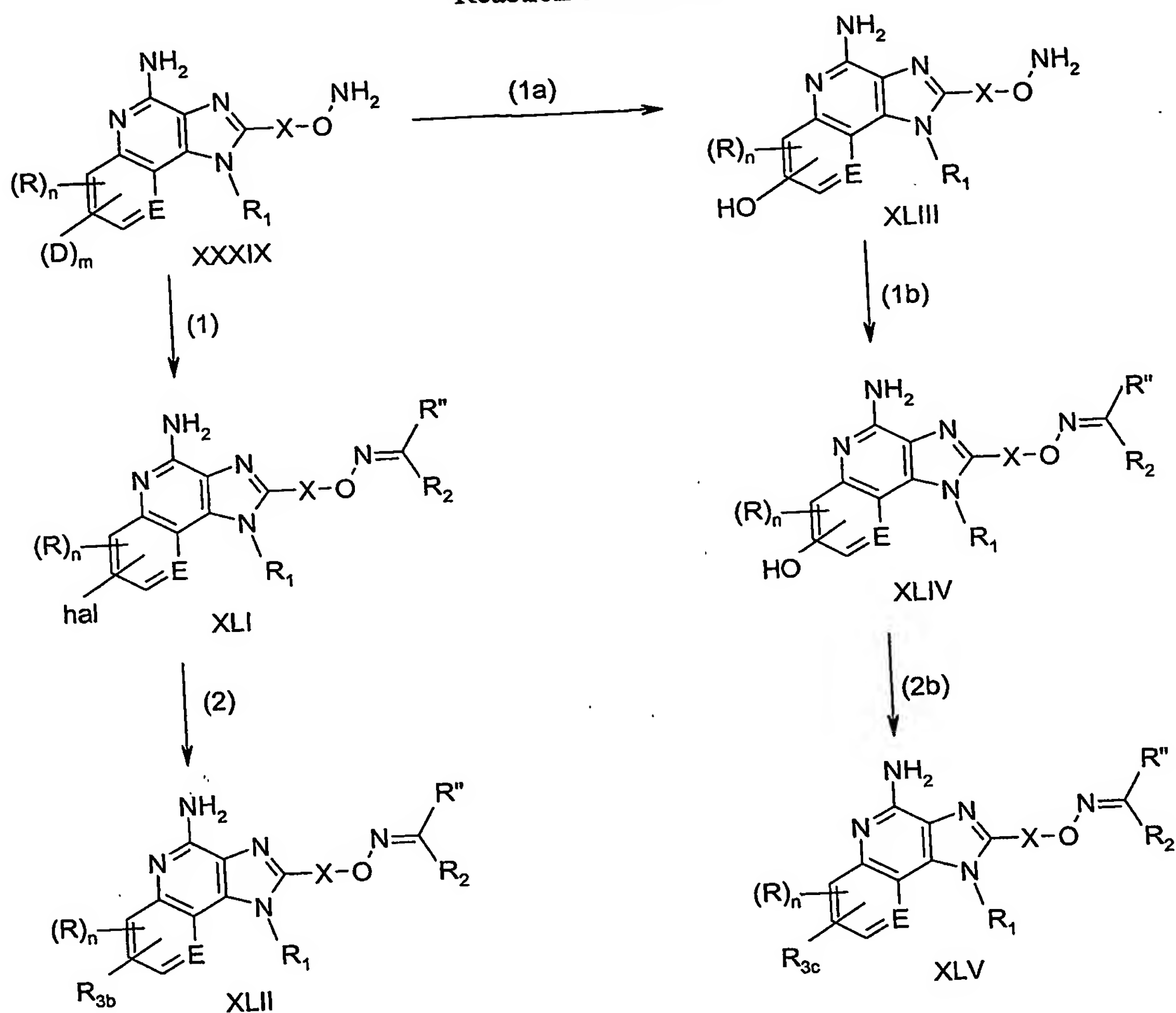
Compounds of Formula XXXIX wherein D is -OCH₂Ph can be converted in Reaction Scheme VI to compounds of Formula XLV wherein R_{3c} is -O-R_{4b}, -O-X'-R₄, -O-X'-Y-R₄, or -O-X'-R₅; wherein R₄, R_{4b}, R₅, X', and Y are as defined above. In step (1a) of Reaction Scheme VI, the benzyl group in a 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XXXIX, wherein D is -OCH₂Ph, is cleaved to provide a hydroxy group. The cleavage is conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium or platinum on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a compound of Formula XXXIX in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the refluxing temperature of the solvent. The product of Formula XLIII or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (1b) of Reaction Scheme VI, a hydroxylamine-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XLIII is converted to an oxime-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XLIV, a subgenus of Formulas I and II, according to the method of step (12) of Reaction Scheme V.

In step (2a) of Reaction Scheme VI, a hydroxy-substituted oxime of Formula XLIV is converted to a compound of Formula XLV, a subgenus of Formula I and II wherein R_{3c} is -O-R_{4b}, -O-X'-R₄, -O-X'-Y-R₄, or -O-X'-R₅, using a Williamson-type ether synthesis. The reaction is effected by treating a hydroxy-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-

amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula XLIV with an aryl, alkyl, or arylalkylenyl halide of Formula Halide-R_{4b}, Halide-alkylene-R₄, Halide-alkylene-Y-R₄, or Halide-alkylene-R₅ in the presence of a base. Numerous alkyl, arylalkylenyl, and aryl halides of these formulas are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, and substituted fluorobenzenes. Other halides of these formulas can be prepared using conventional synthetic methods. The reaction is conveniently carried out by combining an alkyl, arylalkylenyl, or aryl halide with the hydroxy-substituted compound of Formula XLIV in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C, depending on the reactivity of the halide reagent. Alternatively, step (2a) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide prepared from the hydroxy-substituted compound of Formula XLIV reacts with an aryl halide in the presence of copper salts, to provide a compound of Formula XLV, where R_{3c} is -O-R_{4b}, -O-X'_f-R₄, or -O-X'_f-Y-R₄, wherein X'_f is an arylene or heteroarylene. Numerous substituted and unsubstituted aryl halides are commercially available; others can be prepared using conventional methods. The product of Formula XLV, prepared by either of these methods, or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VI



For some embodiments, compounds of the invention are prepared according to Reaction Scheme VII, where R_1 , R_2 , R'' , R_{A2} , R_{B2} , X , and Hal are as defined above, and Ph is phenyl. In step (1) of Reaction Scheme VII, a 2,4-dichloro-3-nitropyridine of Formula XLVI is reacted with an amine of the Formula H_2N-R_1 to form a 2-chloro-3-nitropyridine of Formula XLVII. The reaction is conveniently carried out by combining an amine of Formula H_2N-R_1 and a 2,4-dichloro-3-nitropyridine of Formula XLVI in the presence of a base such as triethylamine in an inert solvent such as DMF. The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods. Many amines of Formula H_2N-R_1 are commercially available; others can be prepared by known synthetic methods. Many 2,4-dichloro-3-nitropyridines of the Formula XLVI are known and can be readily prepared using known

synthetic methods (see, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein).

5 In step (2) of Reaction Scheme VII, a 2-chloro-3-nitropyridine of Formula XLVII is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XLVIII. The reaction can be carried out by combining the compound of Formula XLVII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium(III) chloride, preferably cerium(III) chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction
10 can be carried out by combining the compound of Formula XLVII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50-60 °C, optionally in the presence of ammonium chloride. The product can be isolated from the reaction mixture using conventional methods.

15 In step (3) of Reaction Scheme VII, an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XLVIII is reduced to provide a compound of Formula XLIX. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as palladium on carbon or platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, acetonitrile, or ethyl acetate. The reaction can be carried out at ambient temperature, and the product can be
20 isolated using conventional methods.

In step (4) of Reaction Scheme VII, a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XLIX, is reacted with a carboxylic acid or an equivalent thereof to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula L. The carboxylic acid or equivalent is selected such that it will provide the desired -X-Hal substituent in a compound of Formula L. The reaction can be carried out as described in step (7) of Reaction Scheme V. The
25 product can be isolated using conventional methods.

In step (5) of Reaction Scheme VII, a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula L is treated with *N*-hydroxyphthalimide to provide a compound of Formula LI, which contains a *N*-phthalimide-protected hydroxylamine. The reaction is conveniently carried out as described in step (4) of Reaction Scheme I. The product or a
30 pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme VII, the *N*-phthalimide-protected hydroxylamine of Formula LI is treated with hydrazine in a suitable solvent such as ethanol to provide a hydroxylamine of Formula LII. The reaction can be carried out at ambient temperature and the product can be isolated from the reaction mixture using conventional methods.

5 In step (7) Reaction Scheme VII, the hydroxylamine group in a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula LII reacts with an aldehyde or ketone of Formula $R_2C(O)R''$ to provide an oxime of Formula VIII. The reaction can be carried out using the conditions described above in step (6) of Reaction Scheme I and the product can be isolated from the reaction mixture using conventional methods.

10 In step (8) of Reaction Scheme VII, the tetrazolo ring is removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula VIII by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula LIII. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature.

15 In step (9) of Reaction Scheme VII, an *N*-triphenylphosphinyl intermediate of Formula LIII is hydrolyzed to provide an oxime-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula VI. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol or an alkanol/water solution in the presence of an acid such as trifluoroacetic acid, acetic acid, or hydrochloric acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula VI or as a pharmaceutically acceptable salt thereof.

20 For some embodiments, compounds shown in Reaction Scheme VII can be further elaborated using conventional synthetic methods. For Example, amines of Formula R_1-NH_2 , used in step (1) of Reaction Scheme VII, may contain a protected functional group, such as a *tert*-butoxycarbonyl-protected amino group. The protecting group may be removed later in Reaction Scheme VII after step (4) to reveal, for example, an amine on the R_1 group of a compound of Formula L. An amino group introduced in this manner may be further functionalized by applying the chemistry described in steps (5) and (5a) of

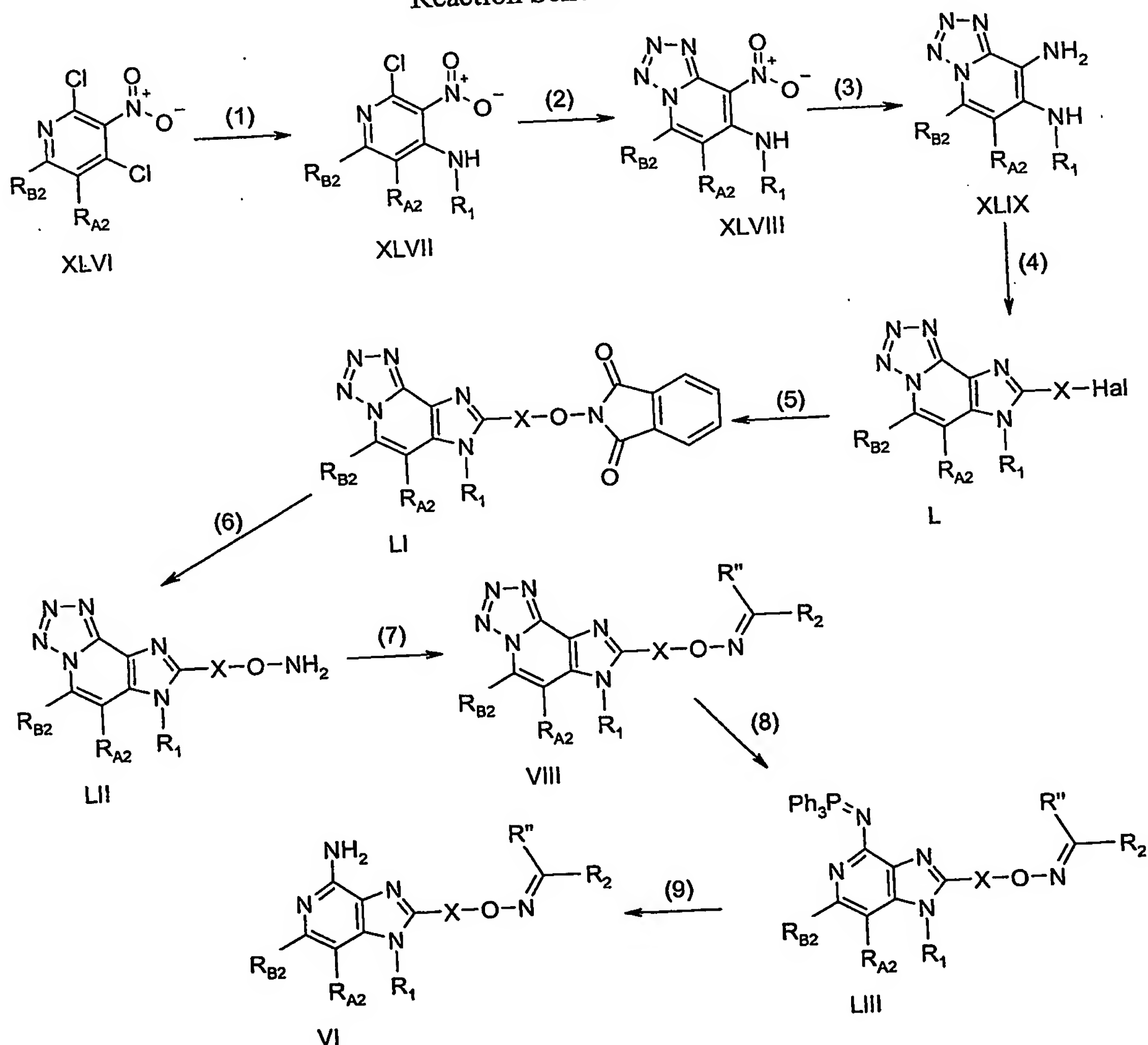
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30 Reaction Scheme II to provide compounds of the Formula L in which R_1 is

$-X'-N(R_8)-Q-R_4$ or $-X'-R_{5a}$, which can be converted into compounds of the Formula VI using the chemistry described in steps (5) – (9) of Reaction Scheme VII. Alternatively, the protecting group may be removed after step (7) of Reaction Scheme VII to reveal an amine on the R_1 group of a compound of Formula VIII. The amino group may be further functionalized as described above to provide compounds of the Formula VIII in which R_1 is $-X'-N(R_8)-Q-R_4$ or $-X'-R_{5a}$, which can be converted into compounds of the Formula VI using the chemistry described in steps (8) and (9) of Reaction Scheme VII.

Compounds of the Formula VI in which R_1 is $-X''-O-N=C(R_1')(R_1'')$ or $-X''-O-NR_{1a}-Y'-R_{1b}$ can be synthesized from compounds shown in Reaction Scheme VII using the chemistry described above in association with Reaction Scheme V.

Reaction Scheme VII



Pharmaceutical Compositions and Biological Activity

5 Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

10 The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100

15 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μ g/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

20 The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

25 Compounds or salts of the invention have been shown to induce the production of certain cytokines and certain compounds or salts of the invention may inhibit the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering

30 them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon- α (IFN- α) and/or tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN- γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor- α (TNF- α). Among other effects, inhibition of TNF- α production can provide prophylaxis or therapeutic treatment of TNF- α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF- α biosynthesis in an animal comprising administering an

effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF- α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus *Escherichia*, *Enterobacter*, *Salmonella*, *Staphylococcus*, *Shigella*, *Listeria*, *Aerobacter*, *Helicobacter*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Streptococcus*, *Chlamydia*, *Mycoplasma*, *Pneumococcus*, *Neisseria*, *Clostridium*, *Bacillus*, *Corynebacterium*, *Mycobacterium*, *Campylobacter*, *Vibrio*, *Serratia*, *Providencia*, *Chromobacterium*, *Brucella*, *Yersinia*, *Haemophilus*, or *Bordetella*;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carinii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

5 (d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

10 (e) T_H2 -mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

15 (g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, an IRM compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or
20 bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B,
25 parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

30 Certain IRM compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, certain

compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg.

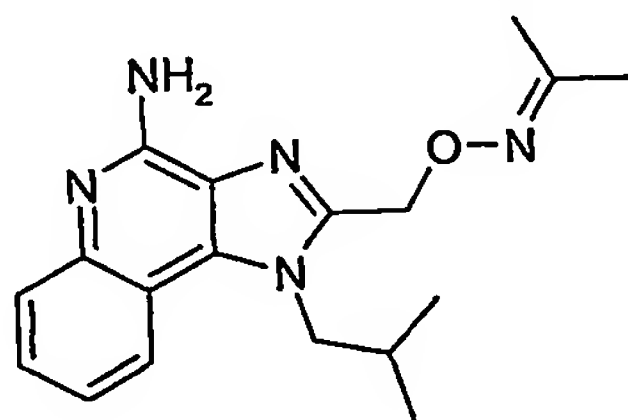
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

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Example 1

Propan-2-one *O*-{[4-amino-1-(2-methylpropyl)-
1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime



10 Part A

*N*⁴-(2-Methylpropyl)quinoline-3,4-diamine (41 g), dichloromethane (550 mL), triethylamine (40 mL, 1.5 eq), and chloroacetyl chloride (16.7 mL, 1.1 eq.) were combined and then stirred at ambient temperature over the weekend. The reaction mixture was diluted with 1,2-dichloroethane (75 mL) and then washed with saturated aqueous sodium bicarbonate (3 x 400 mL). The organic layer was dried over magnesium sulfate, filtered
15 through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 52.81 g of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a brown solid.

Part B

20 3-Chloroperoxybenzoic acid (mCPBA) (16.4 g of 77% max, 73.1 mmol) was added to a solution of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (10 g, 36.5 mmol) in chloroform (250 mL). The reaction mixture was stirred at ambient temperature overnight. Ammonium hydroxide (100 mL) was added and the reaction was stirred vigorously for 15 minutes. *Para*-toluenesulfonyl chloride (8.4 g, 43.8 mmol) was
25 added in portions over a period of 10 minutes. The reaction mixture was stirred at ambient temperature for 1 hour and then filtered to remove a precipitate. The filtrate was

transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 16 g of crude product as a yellow foam. The foam was dissolved in 10% methanol in dichloromethane (20 mL). The solution was divided and loaded onto two FLASH 40+M silica cartridges (90 g), (available from Biotage, Inc, Charlottesville, Virginia, USA). The cartridges were eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 2% methanol in 1:1 ethyl acetate:hexanes, and 5% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 6.4 g of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an orange foam.

Part C

Triethylamine (536 mg, 5.19 mmol) was added to a solution of *N*-hydroxyphthalimide (678 mg, 4.16 mmol) in *N,N*-dimethylformamide (DMF); after 5 minutes a solution of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1 g) in DMF (10 mL) was added. The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50 mL) and then washed with water (1 x 100 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and ethyl acetate (1 x 50 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 1.8 g of crude product as a yellow solid. The solid was dissolved in 5% methanol in chloroform (10 mL) and loaded onto a FLASH 40+M silica cartridge (90 g). The cartridge was eluted sequentially with 1L 1% methanol in chloroform and 3% methanol in chloroform. The fractions containing the desired product were combined and then concentrated under reduced pressure to provide 950 mg of a yellow solid. This material was recrystallized from acetonitrile, isolated by filtration, washed sequentially with acetonitrile and diethyl ether, and then dried in a vacuum oven at 65 °C overnight to provide 640 mg of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}isoindole-1,3-dione as a yellow crystalline solid, mp 221-222 °C.

¹H NMR (300 MHz, DMSO-d₆) δ 8.10 (d, *J* = 7.6 Hz, 1H), 7.88 (s, 4H), 7.63 (dd, *J* = 8.3 Hz, 1.2 Hz, 1H), 7.48 (m, 1H), 7.32 (m, 1H), 6.69 (br s, 2H), 5.51 (s, 2H), 4.73 (d, *J* = 7.6 Hz, 2H), 2.35 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 6H);

MS (APCI) *m/z* 448.0 (M + H)⁺;

5 Anal. Calc'd for C₂₃H₂₁N₅O₃•0.5CH₃CN•0.5H₂O: C, 64.78; H, 5.32; N, 17.31. Found: C, 64.87; H, 5.28; N, 17.63.

Part D

Hydrazine hydrate (9 mL) was added to a suspension of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}isoindole-1,3-dione (3.9 g) in ethanol (90 mL). The resulting solution was stirred at ambient temperature for 3 hours. The reaction mixture was filtered to remove a precipitate and the filter cake was washed with ethanol and dichloromethane. The filtrate was concentrated under reduced pressure, diluted with aqueous 1N hydrochloric acid (100 mL), and then washed sequentially with dichloromethane (2 x 50 mL) and ethyl acetate (1 x 50 mL). Analysis of the organic washes by LCMS indicated that they did not contain product. The aqueous acidic layer was made basic (~ pH 9) with solid sodium carbonate and then extracted sequentially with dichloromethane (1 x 100 mL), ethyl acetate (1 x 100 mL), and dichloromethane (1 X 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and then concentrated under reduced pressure to provide 2.07 g of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine as a tan foam.

Part E

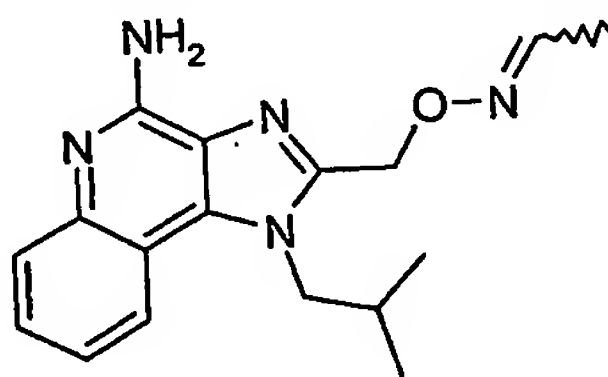
Acetone (3.5 mL) was added to a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (1 g) in methanol (30 mL). The reaction mixture was allowed to stir at ambient temperature for 4 hours and then it was concentrated under reduced pressure. The residue was placed under high vacuum overnight to provide 1.07 g of crude product as a brown foam. The foam was dissolved in dichloromethane (9 mL) and then loaded onto a FLASH 40+S silica cartridge (40 g), (available from Biotage, Inc, Charlottesville, Virginia, USA). The cartridge was eluted sequentially with 500 mL 1:1 ethyl acetate:hexanes, 2% methanol in 1:1 ethyl acetate:hexanes, and 5% methanol 1:1 ethyl acetate:hexanes. The fractions containing

product were combined and concentrated under reduced pressure to provide 690 mg of a yellow solid. This material was recrystallized from ethyl acetate, isolated by filtration, washed with diethyl ether, and then dried under high vacuum to provide 430 mg of propan-2-one *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-

- 5 yl]methyl} oxime as a light yellow crystalline solid, mp 194-195 °C.
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 7.45 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.29 (m, 1H), 6.65 (br s, 2H), 5.30 (s, 2H), 4.48 (d, *J* = 7.6 Hz, 2H), 2.25 (m, 1H), 1.82 (s, 3H), 1.81 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 6H);
¹³C NMR (75 MHz, DMSO-*d*₆) δ 156.2, 152.4, 149.4, 145.6, 133.3, 127.2, 127.0, 126.7,
 10 121.5, 121.0, 115.1, 67.3, 52.2, 29.0, 21.6, 19.6 (2), 15.8;
 MS (APCI) *m/z* 326.2 (*M* + *H*)⁺;
 Anal. Calc'd for C₁₈H₂₃N₅O: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.44; H, 7.14; N, 21.37.

Example 2

15 Acetaldehyde *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime

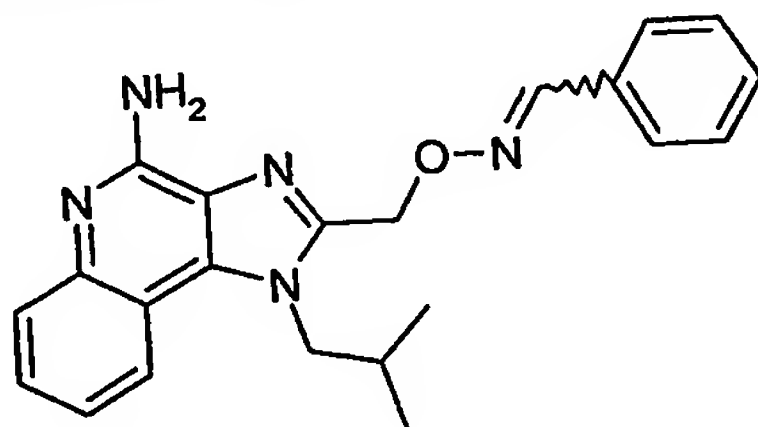


- 20 Acetaldehyde (3.5 mL) was added to a chilled (0 °C) solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (1 g) in methanol (30 mL). The reaction mixture was allowed to warm to ambient temperature and stirred for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was placed under high vacuum overnight to provide 1.37 g of crude product as a
 25 brown foam. An attempt to purify by radial chromatography failed leaving 1.16 g of crude product. This material was dissolved in dichloromethane (6 mL) and then loaded onto a FLASH 40+S silica cartridge (40 g). The cartridge was eluted sequentially with 500 mL 1:1 ethyl acetate:hexanes, 2% methanol in 1:1 ethyl acetate:hexanes, 5% methanol in 1:1

- ethyl acetate:hexanes, and 6% methanol 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 570 mg of a yellow solid. This material was purified by radial chromatography using a 4 mm plate and eluting with 1%, 3%, 5% and 10% methanol in hexanes to provide 480 mg of a yellow solid. This material was recrystallized from acetonitrile; isolated by filtration; washed sequentially with acetonitrile, ethyl acetate, and diethyl ether; and then dried under high vacuum to provide 115 mg of acetaldehyde *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime as a light yellow crystalline solid, mp 155-156 °C.
- ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 7.52 (minor isomer, q, *J* = 5.8 Hz, 0.33H), 7.44 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 7.27 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 6.94 (major isomer, q, *J* = 5.5 Hz, 0.67H), 6.64 (br s, 2H), 5.37 (major isomer, s, 1.33H), 5.30 (minor isomer, s, 0.67H), 4.48-4.44 (m, 2H), 2.31-2.17 (m, 1H), 1.79-1.76 (m, 3H), 0.92 (d, *J* = 6.6 Hz, 6H);
- MS (APCI) *m/z* 312.2 (*M* + *H*)⁺;
Anal. Calc'd for C₁₇H₂₁N₅O: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.29; H, 7.04; N, 22.46.

Example 3

Benzaldehyde *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime



- Benzaldehyde (0.94 mL) was added to a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (2.2 g) in methanol (50 mL). The reaction mixture was stirred at ambient temperature. After 2 hours an additional 1 mL of benzaldehyde was added and the reaction was stirred overnight. The

reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in 10% methanol in chloroform (10 mL) and then loaded onto a FLASH 40+M silica cartridge (90 g). The cartridge was eluted sequentially with 1 L 1:1 ethyl acetate:hexanes, 500 mL 2 %, 3%, 4%, and 5% methanol in 1:1 ethyl acetate:hexanes.

5 The fractions containing product were combined and concentrated under reduced pressure to provide 1.14 g of a tan solid. This material was recrystallized from acetonitrile, isolated by filtration, washed with acetonitrile, and then dried under high vacuum to provide 708 mg of benzaldehyde *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime as a peach crystalline solid, mp 180-181 °C.

10 ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 (s, 1H) 8.04 (d, *J* = 7.8 Hz, 1H), 7.65-7.61 (m, 3H), 7.48-7.41 (m, 4H), 7.31-7.25 (m, 1H), 6.68 (br s, 2H), 5.52 (s, 2H), 4.54 (d, *J* = 7.6 Hz, 2H), 2.35-2.20 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H);

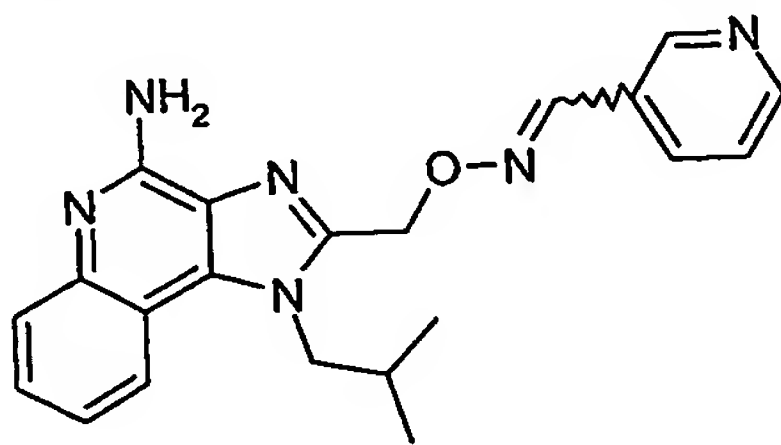
MS (APCI) *m/z* 374.2 (*M* + *H*)⁺;

Anal. Calc'd for C₂₂H₂₃N₅O: C, 70.76; H, 6.21; N, 18.75. Found: C, 70.53; H, 6.20; N,

15 18.75.

Example 4

Pyridine-3-carboxaldehyde *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime Dihydrochloride



20

A solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (2.2 g) in methanol (50 mL) was combined with 3-pyridinecarboxaldehyde (3.6 mL) and stirred at ambient temperature until analysis by LCMS indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure and the residue was loaded onto a FLASH 40+M silica cartridge (90 g). The cartridge was eluted sequentially with 1 L ethyl acetate, 2.5%, 5%, and 10%

25

methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure. The resulting residue was dissolved in dichloromethane (50 mL) and then combined with 4M hydrochloric acid in dioxane (30 mL). A white solid precipitated. The mixture was concentrated and then dissolved in hot ethanol. The ethanol solution was chilled in a freezer over the weekend. The resulting precipitate was isolated by filtration; washed sequentially with ethanol, acetonitrile, and diethyl ether; and then dried under high vacuum to provide 230 mg of pyridine-3-carboxaldehyde *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime dihydrochloride as a tan crystalline solid, mp 213-215 °C.

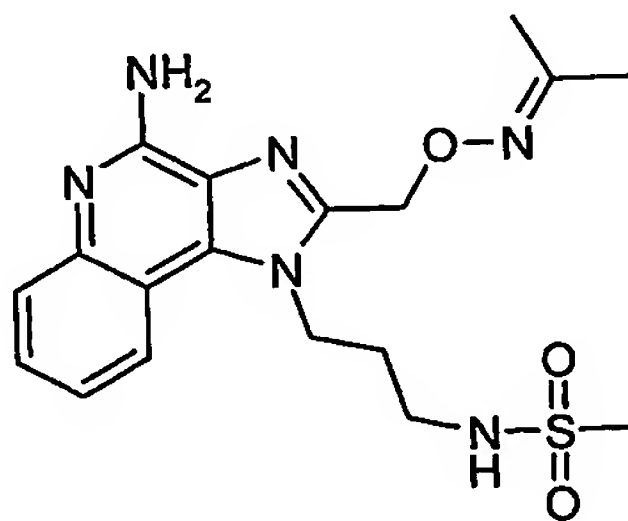
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.83 (m, 1H), 8.58 (s, 1H), 8.42 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 7.85 (m, 2H), 7.74 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.61 (m, 1H), 5.72 (s, 2H), 4.65 (d, *J* = 7.6 Hz, 2H), 2.26 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 151.9, 149.7, 147.5, 146.6, 144.3, 138.8, 135.7, 134.3, 130.3, 129.7, 126.4, 125.4, 125.3, 122.6, 118.9, 112.9, 68.1, 52.6, 29.1, 19.5(2);

MS (APCI) *m/z* 375.1 (*M* + *H*)⁺;

Anal. Calc'd for C₂₁H₂₂N₆O • 2 HCl • 0.5H₂O: C, 56.17; H, 5.79; N, 17.87. Found: C, 56.04; H, 5.75; N, 17.90.

Example 5

N-[3-(4-Amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]methanesulfonamide



Part A

Triethylamine (9 mL, 64.7 mmol) was added to a solution of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)propyl]carbamate (13.65 g, 43.1 mmol) in dichloromethane (150 mL). Chloroacetyl chloride (3.8 mL, 47.5 mmol) was added dropwise over a period of 10

minutes. The reaction mixture was stirred at ambient temperature over the weekend and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and 1:1 water:saturated aqueous sodium bicarbonate. The organic layer was washed with brine (100 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 14.1 g of crude product as a brown foam. The foam was dissolved in a mixture of dichloromethane (15 mL) and methanol (0.5 mL). The solution was divided and loaded onto two FLASH 40+M silica cartridges (90 g). The cartridges were eluted sequentially with 1 L 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, and 10% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and concentrated under reduced pressure to provide 8.96 g of *tert*-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light brown foam.

Part B

3-Chloroperoxybenzoic acid (13.3 g of 77% max, 59.4 eq.) was added in portions over a period of 5 minutes to a solution of *tert*-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (8.9 g, 23.7 mmol) in chloroform (200 mL). The reaction mixture was allowed to stir at ambient temperature overnight. Ammonium hydroxide (50 mL) was added and the reaction mixture was stirred vigorously. *Para*-toluensulfonyl chloride (5.43 g, 28.5 mmol) was added over a period of 5 minutes. The reaction mixture was stirred at ambient temperature for 2 hours; an additional 1 g of *para*-toluensulfonyl chloride was added and the reaction mixture was stirred for another hour. The reaction mixture was filtered to remove solids. The filtrate was transferred to a separatory funnel and the layers were separated. The organic layer was washed with 1:1 water:saturated aqueous sodium bicarbonate (2 x 150 mL). The combined aqueous was extracted with dichloromethane (2 x 150 mL) and ethyl acetate (1 x 100 mL). The combined organic extracts were concentrated under reduced pressure to provide 13.6 g of crude product as a brown foam. The foam was dissolved in dichloromethane (20 mL). The solution was divided and loaded onto two FLASH 40+M silica cartridges (90 g). The first cartridge was eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, and 10% methanol in 1:1 ethyl acetate:hexanes. The second

cartridge was eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 7% methanol in 1:1 ethyl acetate:hexanes, and 7% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 4.3 g of *tert*-butyl [3-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light yellow foam.

Part C

Triethylamine (4.6 mL, 33.1 mmol) was added to a solution of *N*-hydroxyphthalimide (2.16 g, 13.2 mmol) in DMF (10 mL). A solution of *tert*-butyl [3-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (4.3 g, 11.0 mmol) in DMF (20 mL) was added. The reaction was stirred at ambient temperature for 3.5 hours and then diluted with water (100 mL). The resulting precipitate was isolated by filtration, washed with water, and then dried in a vacuum oven at 60°C over the weekend to provide 4.25 g of *tert*-butyl (3-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propyl)carbamate as a light yellow solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.2 (d, *J* = 8.0 Hz, 1H), 7.9 (s, 4H), 7.7 (m, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.2 (m, 1H), 6.7 (br s, 2H), 5.5 (s, 2H), 4.8 (m, 2H), 3.2 (m, 2H), 2.2 (m, 2H), 1.4 (s, 9H);

MS (APCI) *m/z* 517.3 (M + H)⁺.

Part D

Hydrazine hydrate (8 mL of 55%) was added to a suspension of *tert*-butyl (3-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propyl)carbamate (4.25 g, 8.23 mmol) in ethanol (70 mL). The reaction became homogeneous after about 2 minutes. A precipitate started forming after about 1 hour. After stirring at ambient temperature for a total of 2 hours the reaction mixture was filtered and the filter cake was washed with dichloromethane. The filtrate was concentrated under reduced pressure. The residue was azeotroped twice with toluene to provide 3.63 g of *tert*-butyl [3-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a white solid.

Part E

Acetone (20 mL) was added to a solution of *tert*-butyl [3-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (3.6 g) in methanol (70 mL). The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure to provide 4.12 g of *tert*-butyl [3-(4-amino-2-isopropylideneaminoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light yellow foam.

Part F

Trifluoroacetic acid (7 mL) was added to a suspension of *tert*-butyl [3-(4-amino-2-isopropylideneaminoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (4.12 g) in dichloromethane (70 mL). The reaction became homogeneous and was stirred at ambient temperature for 2.5 hours. More trifluoroacetic acid (10 mL) was added and the reaction was stirred for another hour. The reaction mixture was concentrated under reduced pressure and placed under high vacuum overnight to provide 7.68 g of propan-2-one *O*-{[4-amino-1-(3-aminopropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime a white solid. Based on the weight this material was assumed to contain 5 equivalents of trifluoroacetic acid.

Part G

Triethylamine (3.1 mL) was added to a suspension of 2 g of material from Part F in dichloromethane (20 mL) and the reaction became homogeneous. Methanesulfonyl chloride (0.207 mL) was added and the reaction was stirred at ambient temperature. Analysis by LCMS after 1 hour showed that the reaction was not complete. More methanesulfonyl chloride (0.15 mL) was added and the reaction was stirred for an additional 30 minutes. The reaction mixture was washed with saturated aqueous sodium bicarbonate (1 x 40 mL). The aqueous wash was extracted with dichloromethane (2 x 30 mL) and ethyl acetate (1 x 20 mL). The combined organics were washed with brine and then concentrated under reduced pressure to provide 1.5 g of crude product as a tan solid. The solid was dissolved in 10% methanol in chloroform (10 mL) and then loaded onto a FLASH 40+S silica cartridge (40 g). The cartridge was eluted sequentially with 500 mL 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, 2 % methanol in

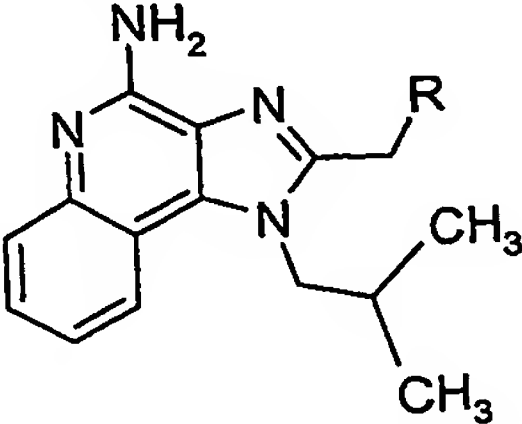
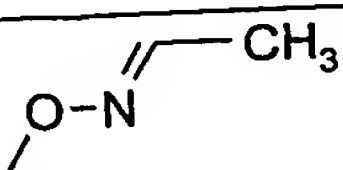
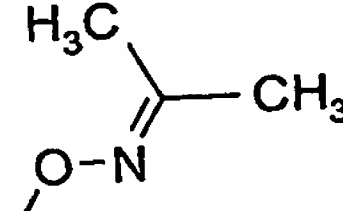
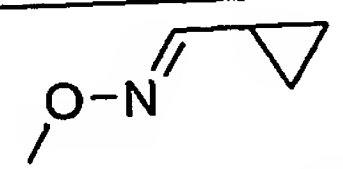
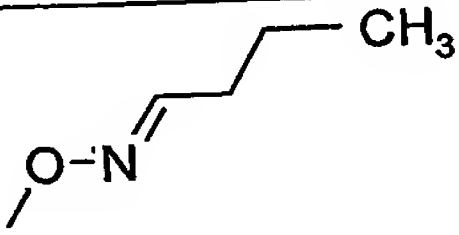
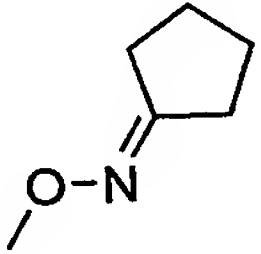
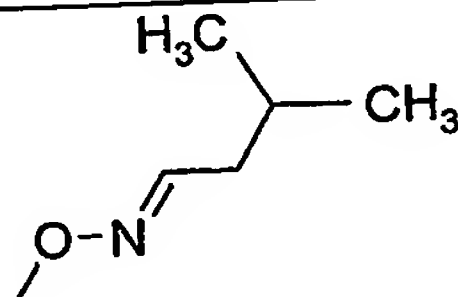
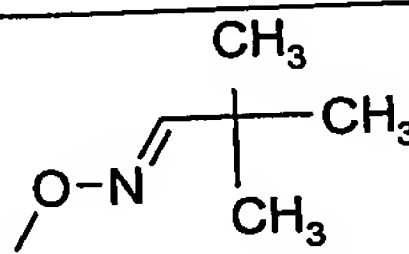
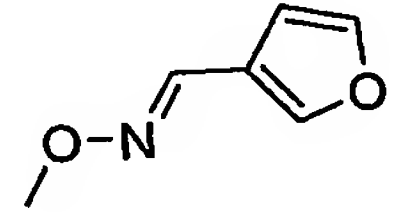
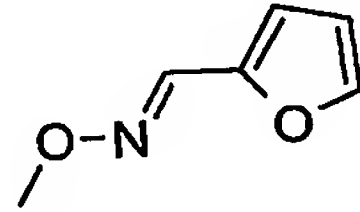
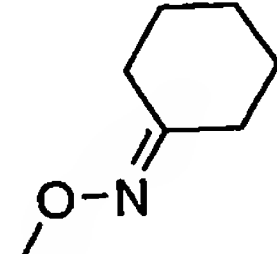
chloroform, and 5 % methanol in chloroform (x3). The fractions containing product were combined and concentrated. The residue was recrystallized from acetonitrile, isolated by filtration, washed with diethyl ether, and then dried under high vacuum to provide 623 mg of *N*-[3-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-

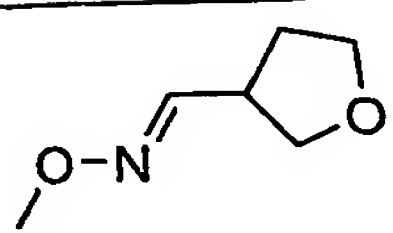
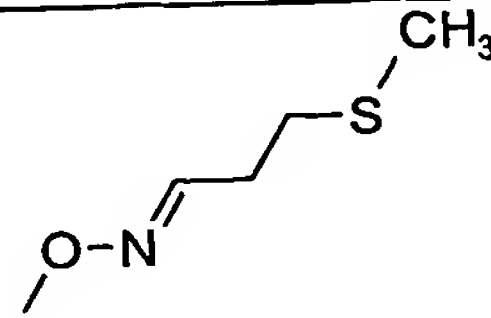
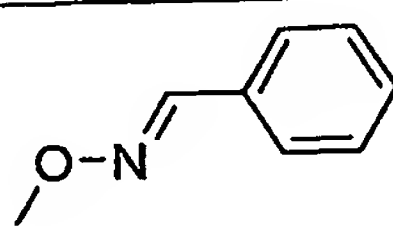
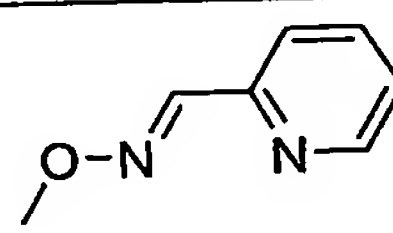
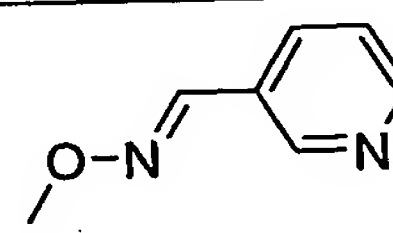
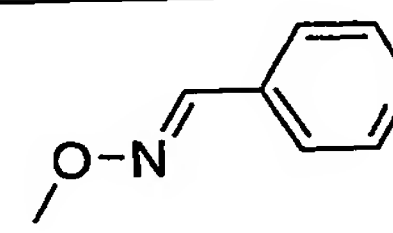
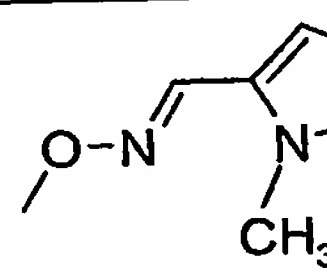
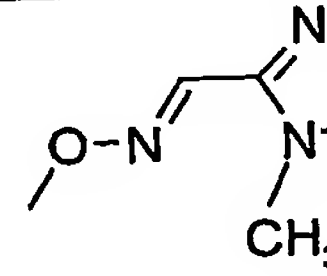
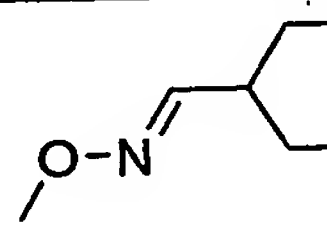
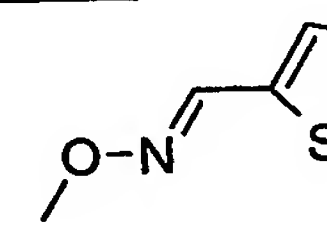
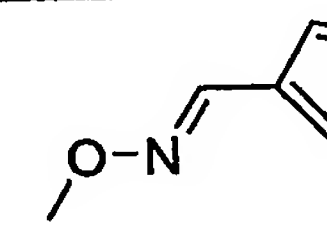
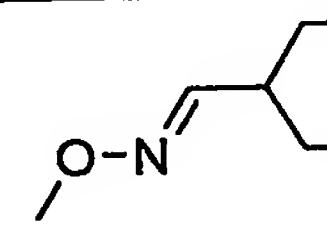
5 yl)propyl]methanesulfonamide as a white crystalline solid, mp 178-179 °C.
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 8.3 Hz, 0.8 Hz, 1H), 7.49-7.43 (m, 1H), 7.30-7.25 (m, 2H), 6.67 (br s, 2H), 5.33 (s, 2H), 4.67 (t, *J* = 7.6 Hz, 2H), 3.17-3.15 (m, 2H), 2.94 (s, 3H), 2.08-2.03 (m, 2H), 1.82 (d, *J* = 7.0 Hz, 6H);
MS (APCI) *m/z* 405.2 (*M* + *H*)⁺;

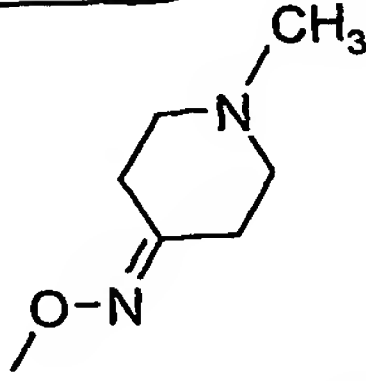
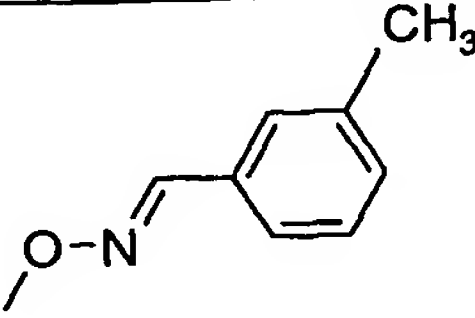
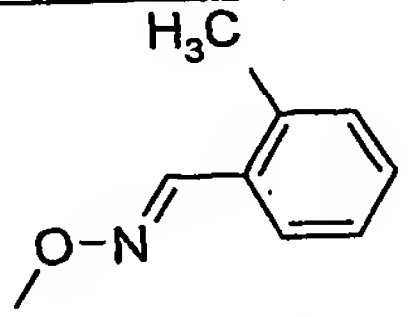
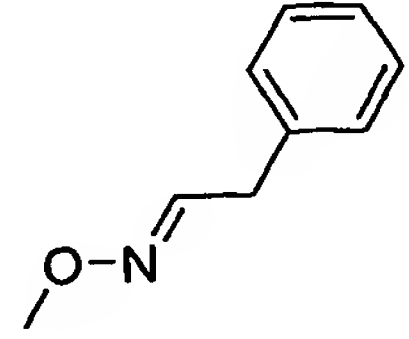
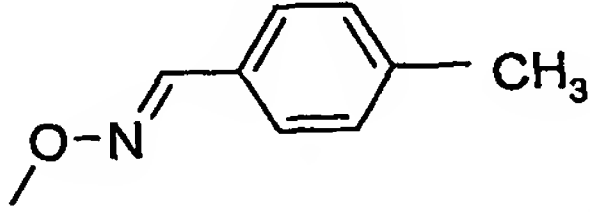
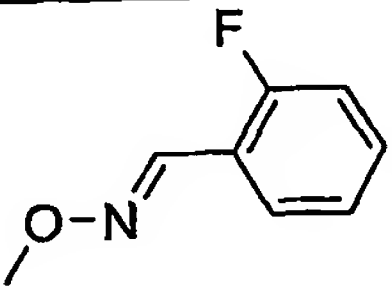
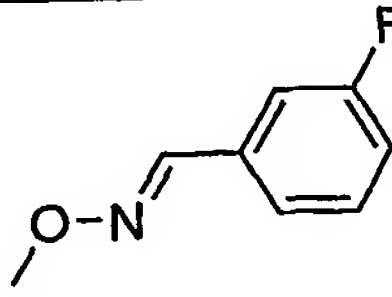
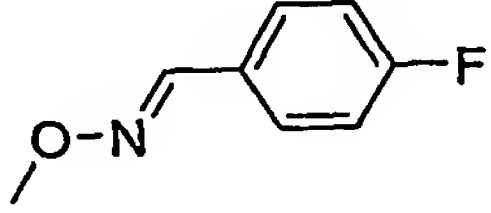
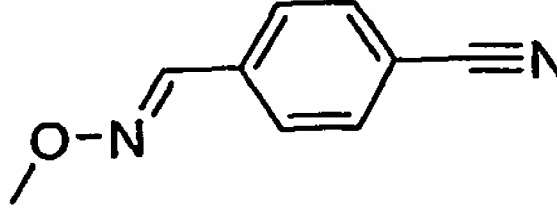
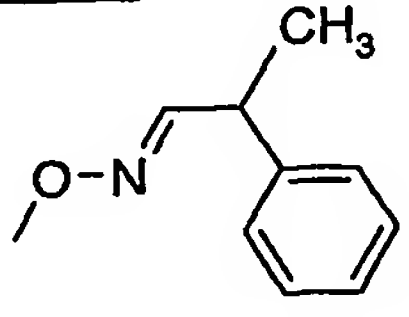
10 Anal. Calc'd for C₁₈H₂₄N₆O₃S: C, 53.45; H, 5.98; N, 20.78. Found: C, 53.35; H, 6.22; N, 20.78.

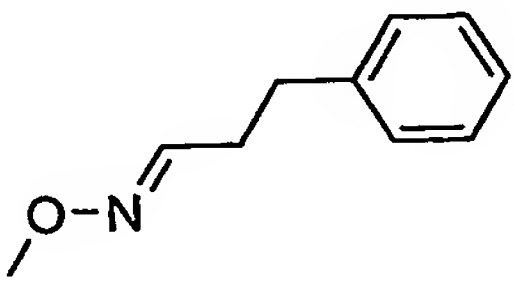
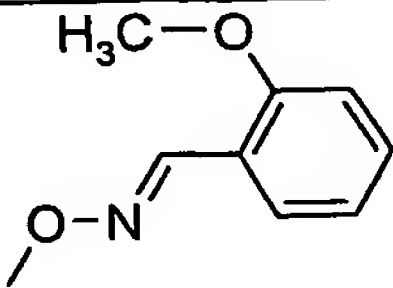
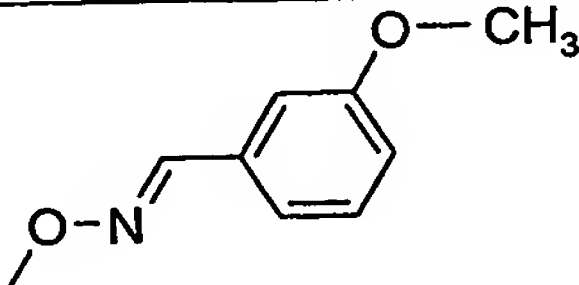
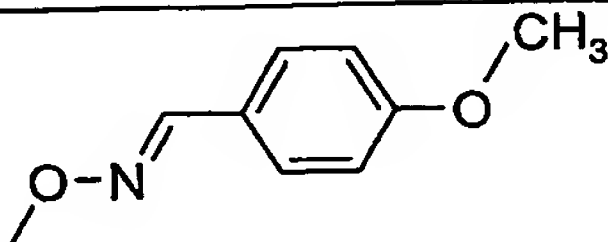
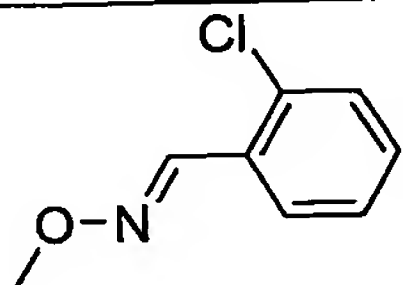
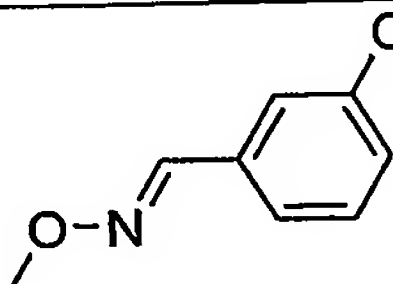
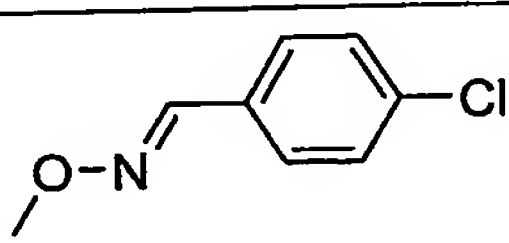
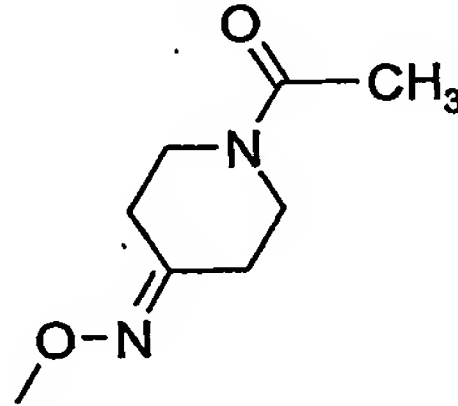
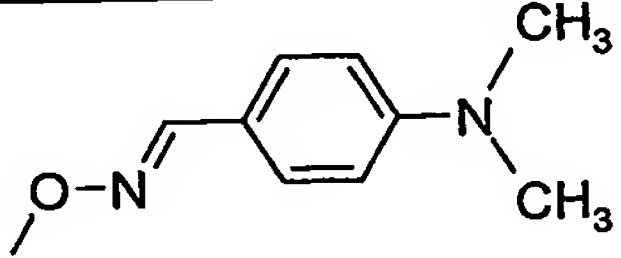
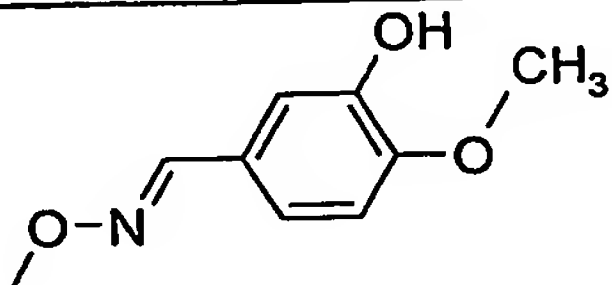
Examples 6 - 51

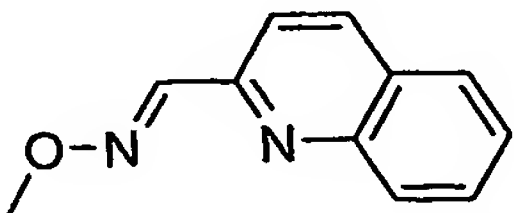
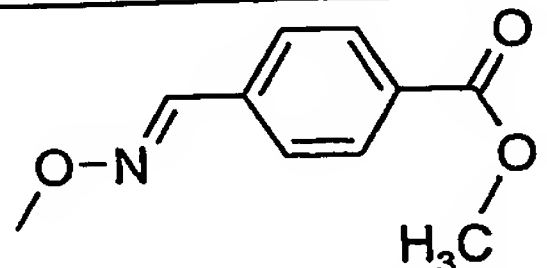
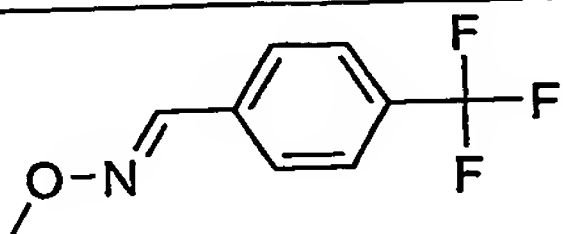
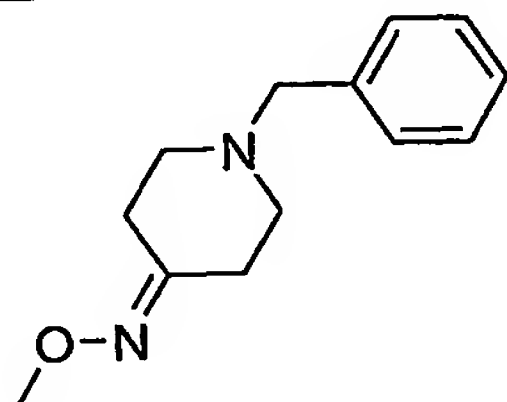
An aldehyde or ketone from the table below (1.1 equivalents) was added to a test
15 tube containing a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (30 mg) in methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction
20 Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Phenomenex LUNA C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size, 100 Angstroms (Å) pore; flow rate: 25 mL/min; non-linear gradient elution from 5-95% B in 9 min, then hold at
25 95% B for 2 min, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the ketone or aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

|  | | | |
|--|----------------------------|---|---------------------------|
| Example | Reagent | R | Measured Mass (M+H) |
| 6 | Acetaldehyde |  | 312.1838 |
| 7 | Acetone |  | 326.1967 |
| 8 | Cyclopropanecarboxaldehyde |  | 338.1985 |
| 9 | Butyraldehyde |  | 340.2103 |
| 10 | Cyclopentanone |  | 352.2126 |
| 11 | Isovaleraldehyde |  | 354.2307 |
| 12 | Trimethylacetaldehyde |  | 354.2303 |
| 13 | 3-Furaldehyde |  | 364.1744 |
| 14 | 2-Furaldehyde |  | 364.1789 |
| 15 | Cyclohexanone |  | 366.2301 |

| | | | |
|----|------------------------------------|---|----------|
| 16 | Tetrahydrofuran-3-carboxaldehyde |  | 368.2054 |
| 17 | 3-(Methylthio)propionaldehyde |  | 372.1864 |
| 18 | Benzaldehyde |  | 374.1983 |
| 19 | Picolinaldehyde |  | 375.1916 |
| 20 | Nicotinaldehyde |  | 375.1934 |
| 21 | Isonicotinaldehyde |  | 375.1952 |
| 22 | 1-Methylpyrrole-2-carboxaldehyde |  | 377.2128 |
| 23 | 1-Methyl-2-imidazolecarboxaldehyde |  | 378.2034 |
| 24 | 3-Cyclohexene-1-carboxaldehyde |  | 378.2255 |
| 25 | 2-Thiophenecarboxaldehyde |  | 380.1561 |
| 26 | 3-Thiophenecarboxaldehyde |  | 380.1558 |
| 27 | Cyclohexanecarboxaldehyde |  | 380.2426 |

| | | | |
|----|-------------------------|---|----------|
| 28 | 1-Methyl-2-piperidone |  | 381.2364 |
| 29 | <i>m</i> -Tolualdehyde |  | 388.2147 |
| 30 | <i>o</i> -Tolualdehyde |  | 388.2126 |
| 31 | Phenylacetaldehyde |  | 388.2146 |
| 32 | <i>p</i> -Tolualdehyde |  | 388.2162 |
| 33 | 2-Fluorobenzaldehyde |  | 392.1895 |
| 34 | 3-Fluorobenzaldehyde |  | 392.1873 |
| 35 | 4-Fluorobenzaldehyde |  | 392.1902 |
| 36 | 4-Cyanobenzaldehyde |  | 399.1962 |
| 37 | 2-Phenylpropionaldehyde |  | 402.2258 |

| | | | |
|----|---------------------------------|---|----------|
| 38 | 3-Phenylpropionaldehyde |  | 402.2316 |
| 39 | 2-Methoxybenzaldehyde |  | 404.2116 |
| 40 | 3-Methoxybenzaldehyde |  | 404.2104 |
| 41 | 4-Methoxybenzaldehyde |  | 404.2098 |
| 42 | 2-Chlorobenzaldehyde |  | 408.1614 |
| 43 | 3-Chlorobenzaldehyde |  | 408.1612 |
| 44 | 4-Chlorobenzaldehyde |  | 408.1581 |
| 45 | 1-Acetyl-4-piperidone |  | 409.2326 |
| 46 | 4-Dimethylaminobenzaldehyde |  | 417.2378 |
| 47 | 3-Hydroxy-4-methoxybenzaldehyde |  | 420.2006 |

| | | | |
|----|-------------------------------|--|----------|
| 48 | 2-Quinolinecarboxaldehyde |  | 425.2097 |
| 49 | Methyl 4-formylbenzoate |  | 432.2004 |
| 50 | 4-Trifluoromethylbenzaldehyde |  | 442.1826 |
| 51 | 1-Benzyl-4-piperidone |  | 457.2686 |

Examples 52 - 59

Part A

- 5 Using the general method of Example 5 Part A, *tert*-butyl [2-(3-aminoquinolin-4-ylamino)ethyl]carbamate (43.5 g, 144 mmol) was reacted with chloroacetyl chloride (17.72 g, 158 mmol) to provide 37.39 g of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part B

- 10 Using the general method of Example 5 Part B, a solution of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (27.45 g, 76.1 mmol) in chloroform (500 mL) was treated with 3-chloroperoxybenzoic acid (25.6 g of 77% max, 114 mmol) and the resulting 5-oxide was aminated using ammonium hydroxide (150 mL) and *para*-toluenesulfonyl chloride (17.4 g, 91.3 mmol) to provide 41.83 g of crude *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a brown solid. A portion (~32 g) of the crude material was dissolved in dichloromethane and then washed with 1 N hydrochloric acid (x3). The organic layer was allowed to stand for several days and a precipitate formed. This material was isolated by filtration to

provide 7.0 g of of *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as an off white solid.

Part C

Using the general method of Example 5 Part C, *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (7 g, 19 mmol) was
5 reacted with *N*-hydroxyphthalimide (3.65 g, 22.3 mmol) to provide 6.37 g of of *tert*-butyl (2-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}ethyl)carbamate as a yellow solid.
10 ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.3 (d, *J* = 8.5 Hz, 1H), 7.9 (s, 4H), 7.6 (m, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.1 (m, 1H), 6.6 (br s, 2H), 5.5 (s, 2H), 4.9 (m, 2H), 3.6 (m, 2H), 1.3 (s, 9H);
MS (APCI) *m/z* 503.2 (*M* + *H*)⁺.

Part D

Using the general method of Example 5 Part D, the *N*-phthalimide protecting group
15 was removed from *tert*-butyl (2-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}ethyl)carbamate (6.35 g) to provide crude
tert-butyl [2-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate .

20 Part E

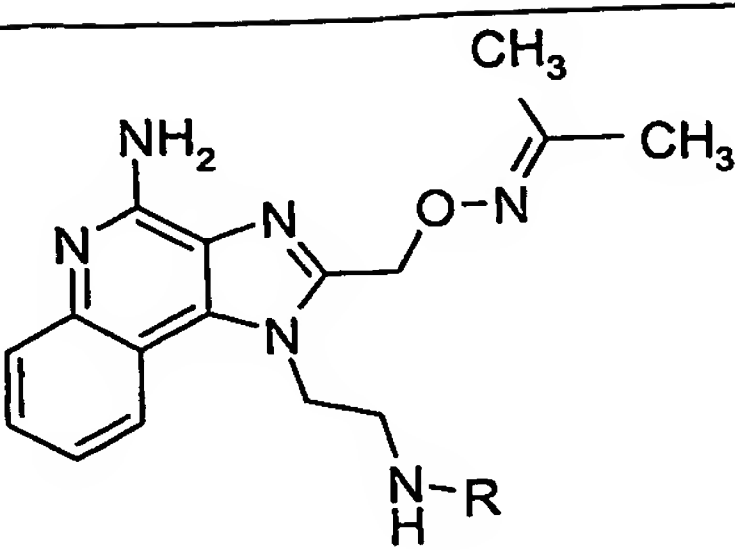
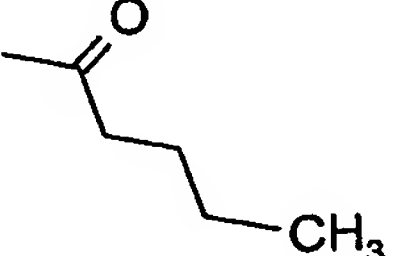
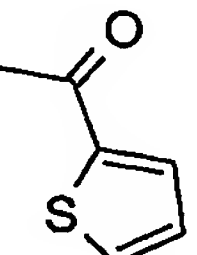
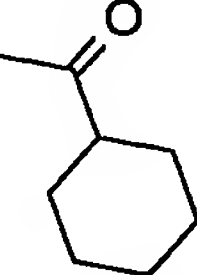
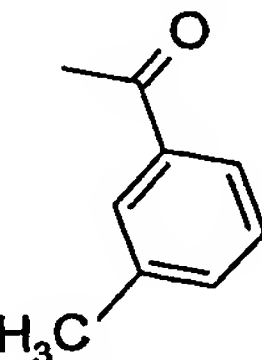
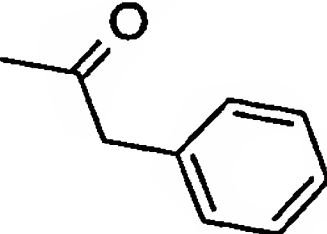
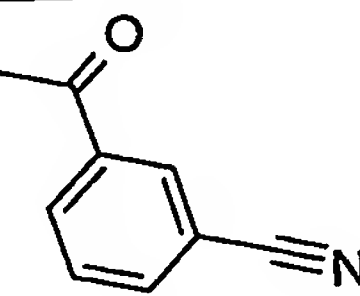
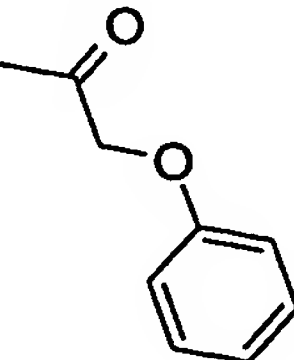
Acetone (25 mL) was added to a suspension of the crude material from Part D in
methanol (100 mL). The resulting solution was stirred at ambient temperature for 3 hours
and then concentrated under reduced pressure. The residue was azeotroped once with
toluene, slurried with ethanol (100 mL) and then filtered. The filter cake was washed with
25 additional ethanol. The filtrate was concentrated under reduced pressure to provide 3.9 g
of product as a yellow solid. Additional product (0.9 g) was obtained by extracting the
filter cake with dichloromethane. The two lots were combined to provide 4.8 g of *tert*-
butyl [2-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

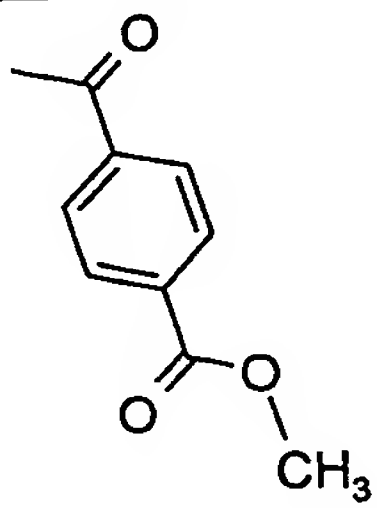
Part F

Trifluoroacetic acid (10 mL) was added to a suspension of *tert*-butyl [2-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (4.8 g) in dichloromethane (100 mL). The reaction became homogeneous and was stirred at ambient temperature. At 2.5 hours and 3.5 hours more trifluoroacetic acid (10 mL and 5 mL respectively) was added. After a total reaction time of 4 hours the reaction mixture was concentrated under reduced pressure. The residue was azeotroped with toluene (x3) and then placed under high vacuum overnight to provide 9.97 g of propan-2-one *O*-{[4-amino-1-(2-aminoethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime as a yellow solid. Based on the weight this material was assumed to contain 5 equivalents of trifluoroacetic acid.

Part G

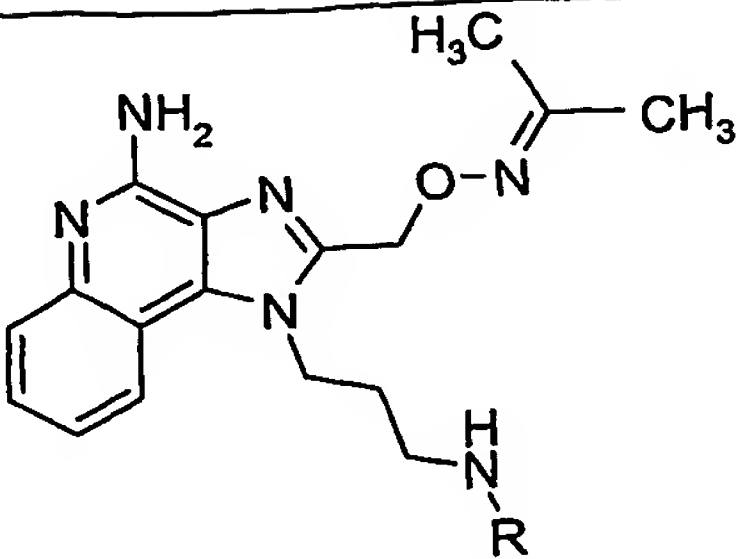

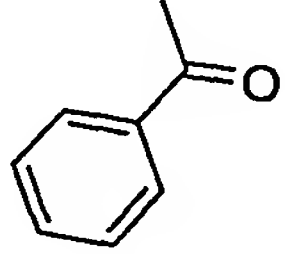
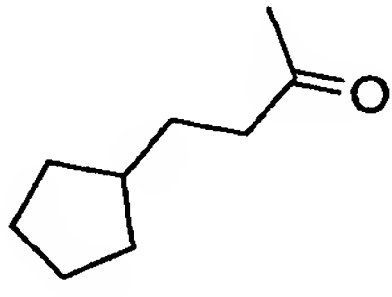
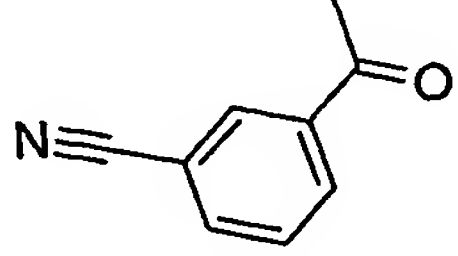
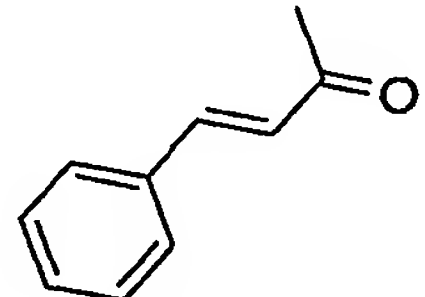
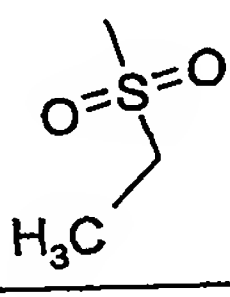
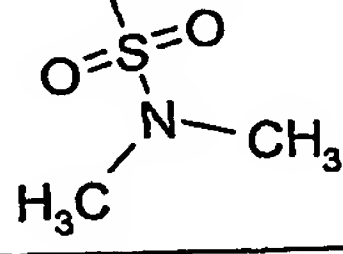
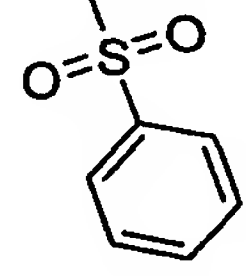
An acid chloride, sulfonyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing propan-2-one *O*-{[4-amino-1-(2-aminoethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime trifluoroacetate (~90 mg) prepared in Part F, *N,N*-diisopropylethylamine (350 μ L, 10 equivalents), and chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system as described for Examples 6 - 51 above. The table below shows the acid chloride, sulfonyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

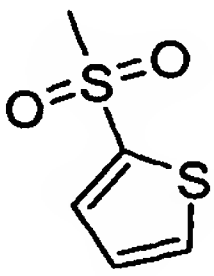
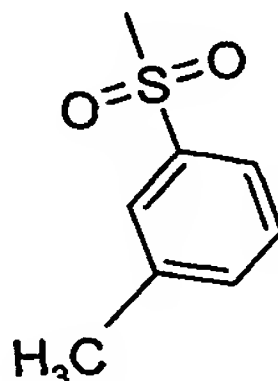
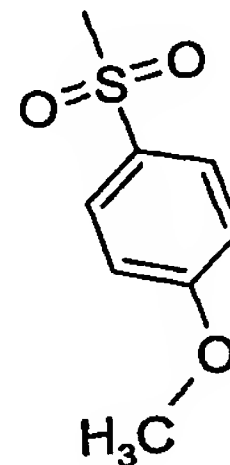
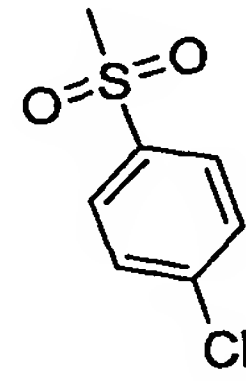
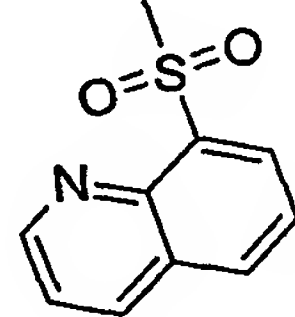
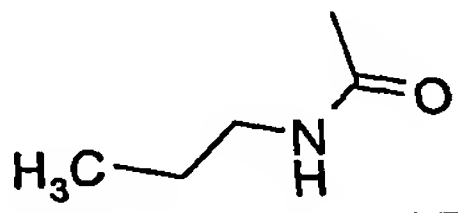
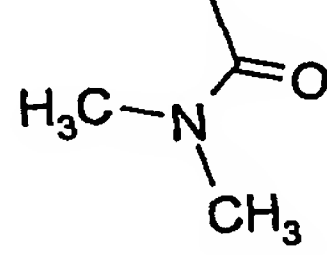
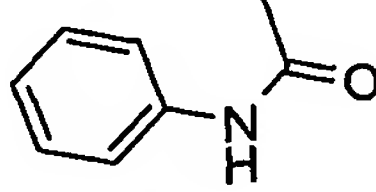
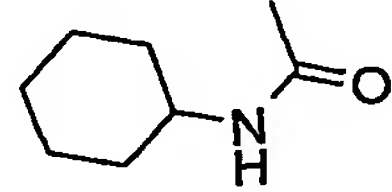
|  | | | |
|--|-------------------------------|---|---------------------|
| Example | Reagent | R | Measured Mass (M+H) |
| 52 | Pentanoyl chloride |  | 397.2346 |
| 53 | Thiophene-2-carbonyl chloride |  | 423.1625 |
| 54 | Cyclohexanecarbonyl chloride |  | 423.2494 |
| 55 | <i>m</i> -Toluoyl chloride |  | 431.2170 |
| 56 | Phenylacetyl chloride |  | 431.2194 |
| 57 | 3-Cyanobenzoyl chloride |  | 442.2014 |
| 58 | Phenoxyacetyl chloride |  | 447.2150 |

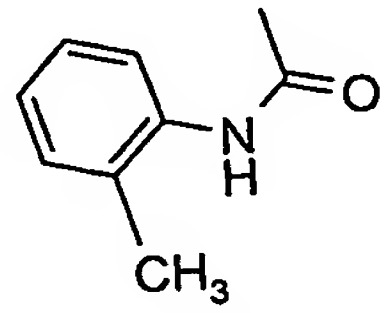
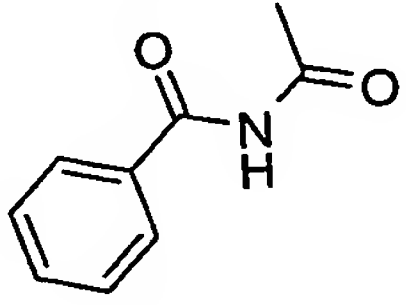
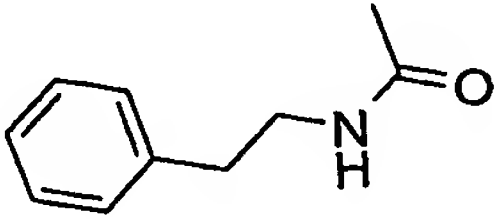
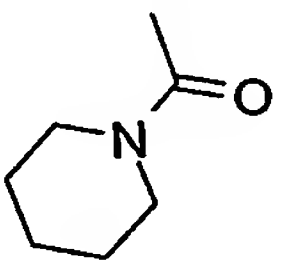
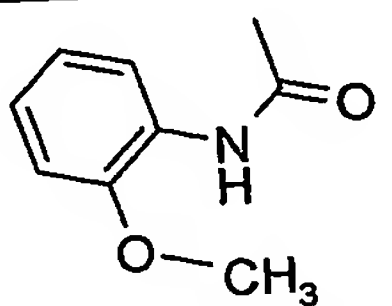
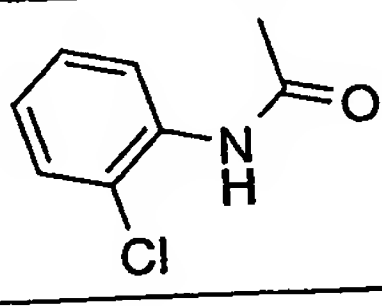
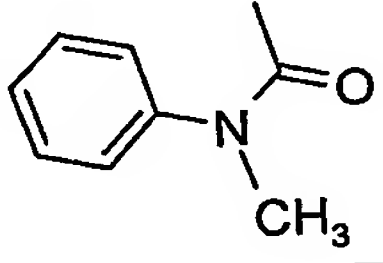
| | | | |
|----|----------------------------------|---|----------|
| 59 | Methyl 4-chlorocarbonyl benzoate |  | 475.2063 |
|----|----------------------------------|---|----------|

Examples 60 - 83

- 5 An acid chloride, sulfonyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing propan-2-one *O*-{[4-amino-1-(3-aminopropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime trifluoroacetate (90 mg), *N,N*-diisopropylethylamine (350 μ L, 10 equivalents), and chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight
- 10 (approximately 18 hours). Water (1 drop) was added and then the solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system as described for Examples 6 - 51 above. The table below shows the acid chloride, sulfonyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of
- 15 the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

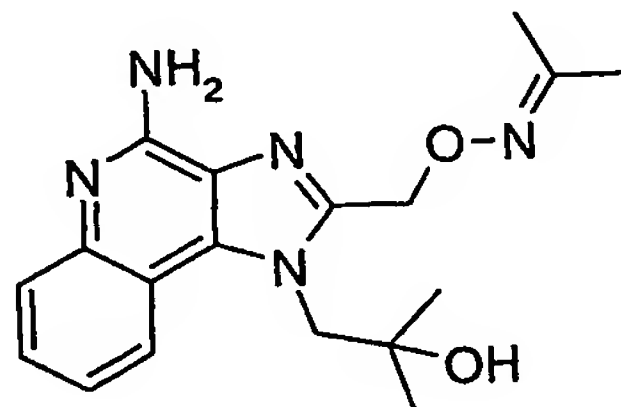
|  | | | |
|--|----------------------------------|---|---------------------|
| Example | Reagent | R | Measured Mass (M+H) |
| 60 | Pentanoyl chloride |  | 411.2507 |
| 61 | Benzoyl chloride |  | 431.2166 |
| 62 | 3-Cyclopentanepropionyl chloride |  | 451.2781 |
| 63 | 3-Cyanobenzoyl chloride |  | 456.2137 |
| 64 | Cinnamoyl chloride |  | 457.2330 |
| 65 | Ethanesulfonyl chloride |  | 419.1870 |
| 66 | Dimethylsulfamoyl chloride |  | 434.1965 |
| 67 | Benzenesulfonyl chloride |  | 467.1851 |

| | | | |
|----|--|---|----------|
| 68 | 2-Thiophenesulfonyl chloride |  | 473.1393 |
| 69 | 3-Methylbenzenesulfonyl chloride |  | 481.2012 |
| 70 | 4-Methoxybenzenesulfonyl chloride |  | 497.1968 |
| 71 | 4-Chlorobenzenesulfonyl chloride |  | 501.1480 |
| 72 | 8-Quinolinesulfonyl chloride |  | 518.1946 |
| 73 | <i>n</i> -Propyl isocyanate |  | 412.2461 |
| 74 | <i>N,N</i> -Dimethylcarbamoyl chloride |  | 398.2310 |
| 75 | Phenyl isocyanate |  | 446.2270 |
| 76 | Cyclohexyl isocyanate |  | 452.2741 |

| | | | |
|----|--|---|----------|
| 77 | <i>o</i> -Tolyl isocyanate |  | 460.2436 |
| 78 | Benzoyl isocyanate |  | 474.2242 |
| 79 | 2-Phenylethyl isocyanate |  | 474.2615 |
| 80 | 1-Piperidinecarbonyl chloride |  | 438.2611 |
| 81 | 2-Methoxyphenyl isocyanate |  | 476.2399 |
| 82 | 2-Chlorophenyl isocyanate |  | 480.1889 |
| 83 | <i>N</i> -Methyl <i>N</i> -phenylcarbamoyl chloride |  | 460.2442 |

Example 84

Acetone *O*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime



5 Part A

Triethylamine (50.0 mL, 360 mmol) was added to a suspension of 4-chloro-3-nitroquinoline (50.0 g, 240 mmol) in DMF (200 mL), followed by dropwise addition of a solution of 1-amino-2-methyl-propan-2-ol (23.5 g, 264 mmol) in DMF (50 mL). The reaction mixture was stirred overnight at room temperature, then water (500 mL) was added and stirring was continued for 30 minutes. A solid was isolated by filtration, washed with water, and dried to yield 60.9 g of 2-methyl-1-[(3-nitroquinolin-4-yl)amino]propan-2-ol, which was used without further purification.

15 Part B

A mixture of 2-methyl-1-[(3-nitroquinolin-4-yl)amino]propan-2-ol (60.9 g, 233 mmol), 5% platinum on carbon (6.1 g), and ethanol (500 mL) was hydrogenated on a Parr apparatus at 30 psi (2.1×10^5 Pa) for 3 hours. The mixture was filtered through CELITE filter agent, which was subsequently rinsed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure to yield an oil that was concentrated twice from toluene to afford 56.6 g of a brown oil that was used directly in the next step.

25 Part C

Triethylamine (49.0 mL, 350 mmol) was added to a stirred suspension of the material from Part B in dichloromethane (450 mL). A solution of chloroacetyl chloride (21.0 mL, 257 mmol) in dichloromethane (50 mL) was added dropwise over 45 minutes. The reaction mixture was stirred for approximately 3 days at room temperature. The solution was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (500 mL) and 1:1 saturated aqueous sodium bicarbonate/water (500 mL).

The aqueous layer was extracted with ethyl acetate (3 x 250 mL) and chloroform (250 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting pale brown solid was crystallized from dichloromethane (80 mL) to afford 25.7 g of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-
5 c]quinolin-1-yl]-2-methylpropan-2-ol as pale yellow crystals. The mother liquor was concentrated and crystallized from dichloromethane (40 mL) to yield an additional 3.56 g of product. The mother liquor was concentrated under reduced pressure and the resulting residue was purified by chromatography using a HORIZON HPFC system (an automated, modular high-performance flash purification product available from Biotage, Inc,
10 Charlottesville, Virginia, USA) (silica gel, gradient elution with 3-13% methanol in ethyl acetate) to afford 15.5 g of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol.

Part D

15 mCPBA (77% pure, 36.5 g, 163 mmol) was added over 10 minutes to a stirred suspension of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (23.6 g, 81.4 mmol) in chloroform (500 mL). The resulting solution was stirred at room temperature for 1.5 hours. Concentrated ammonium hydroxide (200 mL) was added. After 5 minutes, *p*-toluenesulfonyl chloride (18.6 g, 97.7 mmol) was added in portions.
20 The mixture was stirred at room temperature for 2.3 hours, then was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL, then 3 x 200 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a foam. The crude product was purified in portions by chromatography on a HORIZON HPFC
25 system (silica gel, elution with 5% methanol in chloroform followed by gradient elution with 5-15% methanol in chloroform) to yield 9.42 g of 1-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a pale yellow solid.

Part E

30 A solution of 1-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (1.00 g, 3.28 mmol) in DMF (3.0 mL) was added to a solution of *N*-

hydroxyphthalimide (642 mg, 3.94 mmol) and triethylamine (0.915 mL, 6.56 mmol) in DMF (3.0 mL). The flask containing the solution of 1-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol was rinsed with DMF (3.0 mL), which was added to the reaction solution. The solution was stirred at room temperature for 3 hours and a solid formed. The solid was isolated by filtration, washed with dichloromethane, and dried. The off-white solid was dissolved in hot DMF (20 mL). Acetonitrile (50 mL) was added to the solution, which was then placed in a freezer. Crystals formed and were isolated by filtration, washed with acetonitrile, and dried to provide 288 mg of 2-[[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy]-1*H*-isoindole-1,3(2*H*)-dione as orange crystals, mp 270.0-272.0 °C.

Anal calcd. for C₂₃H₂₁N₅O₄: C, 64.03; H, 4.91; N, 16.23. Found: C, 63.65; H, 4.65; N, 16.50.

15 Part F

Hydrazine (20 mL) was added to a stirred suspension of 2-[[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy]-1*H*-isoindole-1,3(2*H*)-dione (14.0 g, 32.4 mmol) in ethanol (100 mL). The mixture was stirred at room temperature and after 5 minutes a solution formed. After 1 hour, a solid began to form and additional ethanol (100 mL) was added. After 4.5 hours, the solid was isolated by filtration, washed with dichloromethane, and dried to yield 9.30 g of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol as a yellow solid, some of which was used without further purification in the next step. Two batches of the product (6.63 g and 1.00 g) were purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-15% of 2 M NH₃ in methanol/chloroform) to provide 4.45 g and 650 mg of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol as a yellow solid, respectively. Some of the chromatographed product (650 mg) was crystallized from acetonitrile to yield 377 mg of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol as pale yellow crystals, mp 178.0-179.0 °C.

Anal calcd. for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.93; H, 6.38; N, 23.40.

Part G

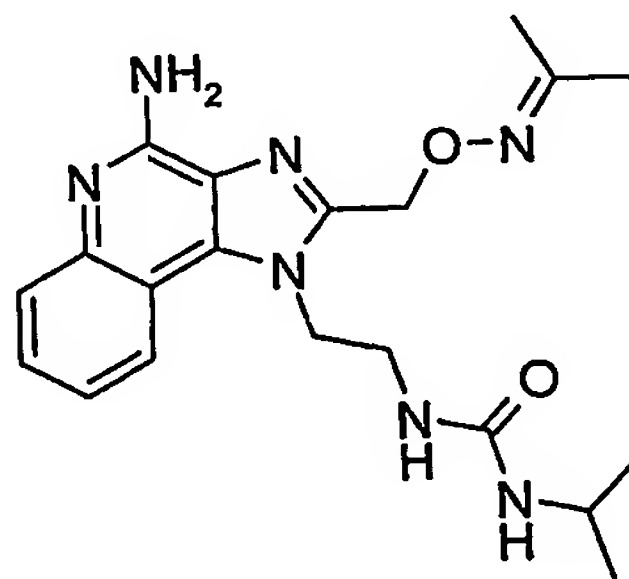
5 A solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (800 mg, 2.65 mmol) in acetone (10 mL) and methanol (10 mL) was stirred for 20 hours at room temperature, then was concentrated under reduced pressure. The resulting yellow solid was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 5-15% methanol in chloroform) followed by
10 crystallization from acetonitrile to yield 400 mg of acetone *O*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime as pale yellow crystals, mp 212-216 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.27 (d, *J* = 8.3 Hz, 1H), 7.60 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.21 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 6.61 (s, 2H), 5.44 (br s, 2H), 4.93 (s, 1H), 4.73 (br s, 2H), 1.80 (s, 3H), 1.78 (s, 3H), 1.17 (br s, 6H);
15 MS (APCI) *m/z* 342.1 (*M* + *H*)⁺;

Anal. calcd for $C_{18}H_{23}N_5O_2$: C, 63.32; H, 6.79; N, 20.51. Found: C, 63.32; H, 7.00; N, 20.65.

Example 85

20 *N*-{2-[4-Amino-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-isopropylurea



25 Isopropyl isocyanate (0.262 mL, 2.66 mmol) was added to a stirred solution of the material prepared in Parts A-F of Examples 52-59 (2.42 mmol) and triethylamine (1.70 mL, 12.1 mmol) in dichloromethane (25 mL) at room temperature. After 10 minutes, a

solid formed. After 1 hour, the reaction mixture was concentrated under reduced pressure to yield a solid that was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 5-25% methanol in chloroform). The appropriate fractions were combined and concentrated under reduced pressure to yield 1.73 g of a white solid that was crystallized from acetonitrile to afford 650 mg of *N*-{2-[4-amino-2-({[(1-methylethylidene)amino]oxy)methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-isopropylurea as a hydrate and partial trifluoroacetate salt, white crystals, mp 230.0-231.0 °C.

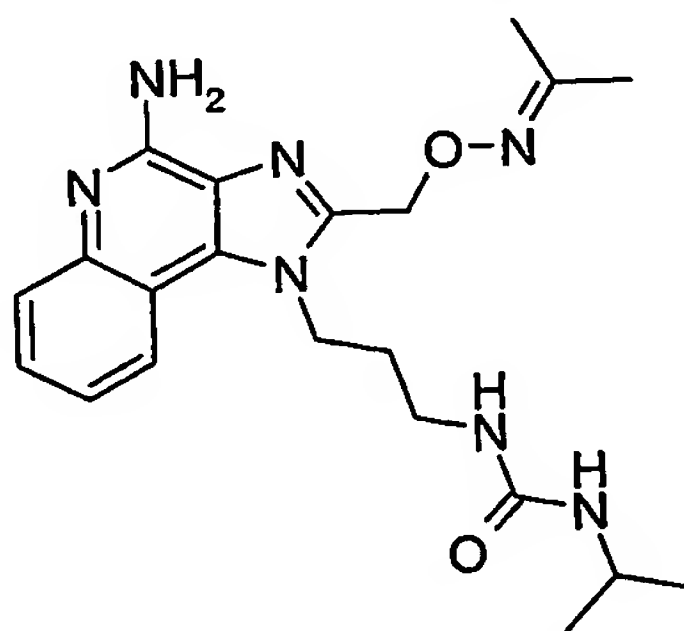
¹H NMR (300 MHz, DMSO-*d*₆) δ 9.17 (br s, 2H), 8.54 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.73 (m, 1H), 7.56 (m, 1H), 6.08 (t, *J* = 5.7 Hz, 1H), 5.92 (d, *J* = 7.8 Hz, 1H), 5.32 (s, 2H), 4.75 (t, *J* = 6.1 Hz, 2H), 3.61 (m, 1H), 3.49 (m, 2H), 1.84 (s, 3H), 1.80 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 6H);

MS (APCI) *m/z* 398.2 (*M* + *H*)⁺;

Anal calcd. for C₂₀H₂₇N₇O₂•0.7 CF₃CO₂H•1.0 H₂O: C, 51.89; H, 6.04; N, 19.80. Found: C, 51.99; H, 5.78; N, 19.74.

Example 86

N-{3-[4-Amino-2-({[(1-methylethylidene)amino]oxy)methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-*N'*-isopropylurea



The method described in Example 85 was used to convert the material prepared in Parts A-F of Example 5 (2.58 mmol) into 440 mg of *N*-{3-[4-amino-2-({[(1-methylethylidene)amino]oxy)methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-*N'*-isopropylurea, which was isolated as the hydrate and partial trifluoroacetate salt, white crystals, mp 184.0-186.0 °C.

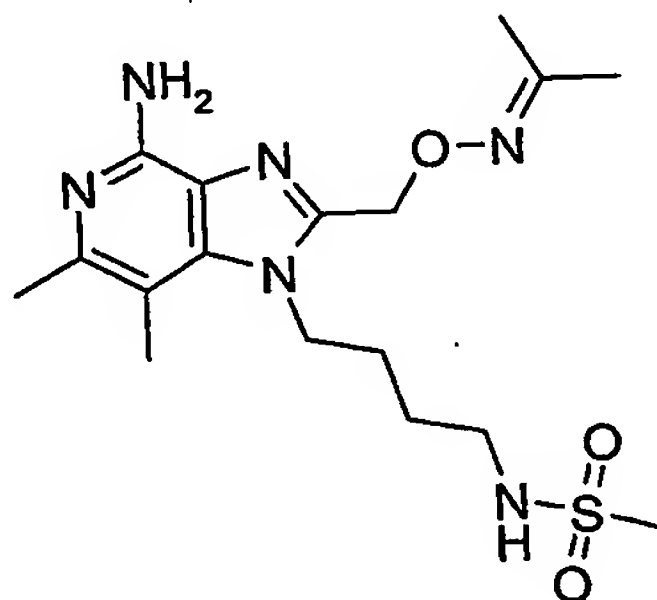
^1H NMR (300 MHz, DMSO- d_6) δ 8.55 (br s, 2H), 8.18 (d, $J = 7.8$ Hz, 1H), 7.77 (dd, $J = 8.4, 1.1$ Hz, 1H), 7.67 (m, 1H), 7.49 (m, 1H), 6.05 (t, $J = 5.8$ Hz, 1H), 5.86 (d, $J = 7.7$ Hz, 1H), 5.34 (s, 2H), 4.65 (t, $J = 7.8$ Hz, 2H), 3.70 (m, 1H), 3.20 (m, 2H), 1.97 (m, 2H), 1.84 (s, 3H), 1.81 (s, 3H), 1.05 (d, $J = 6.6$ Hz, 6H);

5 MS (APCI) m/z 412.2 ($M + H$) $^+$;

Anal calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_7\text{O}_2 \cdot 0.5 \text{CF}_3\text{CO}_2\text{H} \cdot 1.0 \text{H}_2\text{O}$: C, 54.31; H, 6.53; N, 20.15. Found: C, 54.19; H, 6.14; N, 20.13.

Example 87

10 *N*-{4-[4-Amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide



Part A

15 A solution of *tert*-butyl 4-aminobutylcarbamate (8.50 g, 45.2 mmol) in DMF (20 mL) in an addition funnel was added over 1 hour to a stirred solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (10.0 g, 45.2 mmol) and triethylamine (9.30 mL, 67.8 mmol) in DMF (100 mL). The addition funnel was rinsed with DMF (17 mL) and the solution was added to the reaction vessel. After the reaction solution was stirred overnight at room temperature, additional *tert*-butyl 4-aminobutylcarbamate (0.1 equivalent) was added. The solution was allowed to stir an additional 2 hours, then was concentrated under reduced pressure. The resulting oil was partitioned between ethyl acetate (400 mL) and water (100 mL). The organic phase was washed with water (4 x 50 mL), then was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, elution with 33% ethyl acetate in hexanes followed by 66% ethyl acetate in hexanes) to afford 9.2 g of *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate.

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Part B

The purified *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate from A was combined with crude *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate from a similar experiment to yield 38 g (approximately 101 mmol) of material, which was combined with sodium azide (13.0 g, 202 mmol), cerium(III) chloride heptahydrate (19.0 g, 51.0 mmol), and 9:1 acetone/trile/water (300 mL). The reaction mixture was heated at reflux for 3 days, then was allowed to cool to room temperature and was filtered. The filter cake was rinsed with DMF. The filtrate was concentrated under reduced pressure to yield an oil that was purified by flash chromatography (silica gel, elution with 2:1:1 ethyl acetate/hexanes/chloroform, followed by 4:1 ethyl acetate/chloroform) to afford 23 g of *tert*-butyl 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate.

15 Part C

A mixture of *tert*-butyl 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate (9.00 g, 23.7 mmol), 10% palladium on carbon (900 mg), and acetone/trile (100 mL) was hydrogenated on a Parr apparatus for 5 hours. The mixture was filtered through CELITE filter agent, which was rinsed afterwards with methanol. The filtrate was concentrated under reduced pressure to yield 6.70 g of *tert*-butyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate.

Part D

Ethyl 2-chloroethanimidoate hydrochloride (ethyl chloroacetimidate hydrochloride) (2.58 g, 16.4 mmol) was added to a solution of *tert*-butyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate (3.80 g, 10.9 mmol) in chloroform (75 mL). The solution was stirred for 3 days, then saturated aqueous sodium bicarbonate (40 mL) was added. The aqueous phase was extracted with chloroform (3 x 40 mL). The organic phases were combined, washed with water (2 x 20 mL) and saturated aqueous sodium bicarbonate (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 4.3 g of *tert*-butyl 4-[8-(chloromethyl)-5,6-

dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butylcarbamate, which was used in the next step without purification.

Part E

5 *tert*-Butyl 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butylcarbamate (4.05 g, 9.40 mmol) was dissolved in 4 M HCl in dioxane (25 mL). Almost immediately, a solid precipitated and methanol was added (25 mL). After 10 minutes, the reaction mixture was concentrated under reduced pressure and the residue was dried under vacuum. The residue was dissolved in dichloromethane (50 mL) and the solution was cooled to 0 °C, then triethylamine (5.24 mL, 37.6 mmol) was added followed by methanesulfonic anhydride (2.46 g, 14.1 mmol). After 10 minutes, more triethylamine and methanesulfonic anhydride (2 equivalents each) were added and stirring was continued for 50 minutes. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate (20 mL) and dichloromethane (40 mL). The aqueous layer was extracted with dichloromethane (2 x 15 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (2 x 20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield an off-white solid. The solid was dissolved in dichloromethane/chloroform and the solution was transferred to a separatory funnel. The solution was washed with saturated aqueous sodium carbonate, water, and saturated aqueous sodium carbonate. The solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 2.1 g of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}methanesulfonamide.

25 Part F

N-Hydroxyphthalimide (64 mg, 0.39 mmol) was added to a stirred solution of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}methanesulfonamide (100 mg, 0.26 mmol) in DMF (2.6 mL). Triethylamine (0.109 mL, 0.78 mmol) was added dropwise, causing the solution to turn red. After 3 hours, more *N*-hydroxyphthalimide and triethylamine (3 equivalents each) were added and stirring was continued overnight. The solvent was removed under reduced pressure. To

the resulting oil was added ethyl acetate and water, which caused a yellow solid to form. The solid was isolated by filtration, washed with chloroform, and then was triturated with ethyl acetate and isolated by filtration to afford *N*-[4-(8-{{(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy)methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]methanesulfonamide as a yellow solid.

Part G

A mixture of *N*-[4-(8-{{(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy)methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]methanesulfonamide (205 mg, 0.40 mmol), hydrazine hydrate (0.4 mL), and ethanol (4 mL) was stirred for 30 minutes. The solvent was removed under reduced pressure and the residue was partitioned between 1 M aqueous HCl (20 mL) and dichloromethane (10 mL). The aqueous phase was washed with dichloromethane (3 x 8 mL), then was adjusted to pH 12 with 1 M aqueous sodium hydroxide and was concentrated under reduced pressure. To the residue was added acetone (10 mL) and methanol (10 mL), and the reaction mixture was stirred for 3 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (20 mL) and saturated aqueous sodium carbonate (20 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic layers were combined, washed with saturated aqueous sodium carbonate (3 x 10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 20-40% CMA in chloroform, where CMA is 80:18:2 chloroform/methanol/concentrated ammonium hydroxide) to yield 91 mg of *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy)methyl}-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}methanesulfonamide as a white foam.

Part H

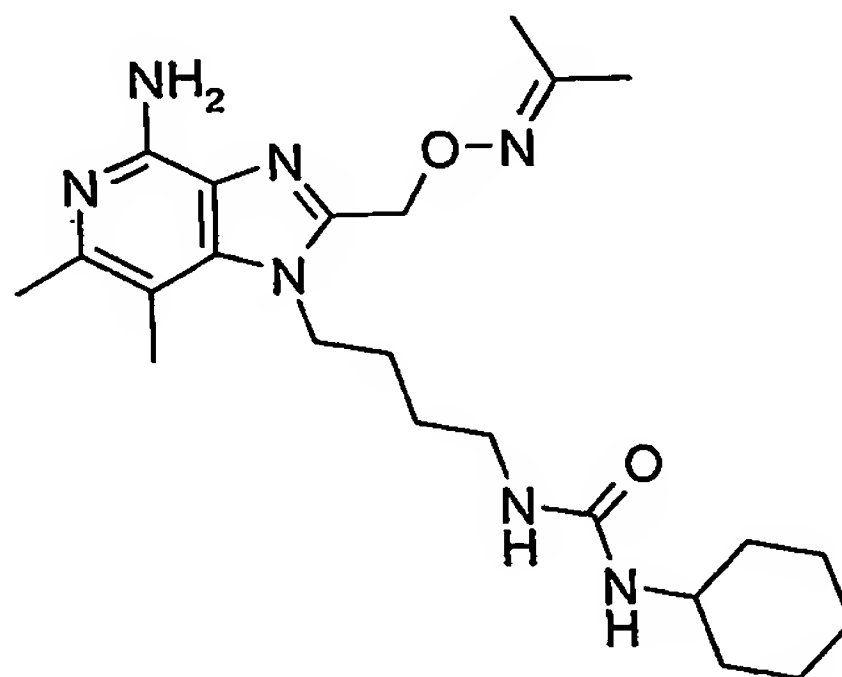
A mixture of *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy)methyl}-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}methanesulfonamide (720 mg, 1.70 mmol), triphenylphosphine (670 mg, 2.55 mmol), and 1,2-dichlorobenzene (15 mL) was heated at 110 °C for 2 days. The solvent was removed under reduced pressure and the

residue was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 15-45% CMA in chloroform) to yield starting material and the ylide product, which were combined and resubmitted to the reaction conditions for 5 days. After 5 days, the temperature was increased to 120 °C and stirring was continued for another day. The reaction was allowed to cool to room temperature and was concentrated under reduced pressure to yield a residue that was purified using the conditions described above to afford the *N*-triphenylphosphinyl ylide product. That material was divided and treated with 1 M HCl in methanol at room temperature or with methanol and water at 60 °C. The two reactions were combined and the methanol was removed under reduced pressure. The acidic aqueous layer was washed with dichloromethane (3 x 5 mL), then was adjusted to a basic pH with sodium carbonate. The mixture was extracted with dichloromethane (3 x 20 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 15-35% CMA in chloroform) followed by crystallization from dichloromethane/heptane to afford 104 mg of *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide as a white powder, mp 157.0-159.0 °C.

Anal. Calcd for C₁₇H₂₈N₆O₃S: C, 51.50; H, 7.12; N, 21.19; Found: C, 51.41; H, 7.22; N, 21.17.

Example 88

N-{4-[4-Amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy)methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-*N'*-cyclohexylurea



5 Part A

Concentrated hydrochloric acid (10 mL) was added to a suspension of *tert*-butyl 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butylcarbamate (prepared in Parts A-D of Example 87, 1.00 g, 2.30 mmol) in methanol (23 mL). The reaction mixture was stirred at room temperature for 2 hours, then was concentrated under reduced pressure to yield a residue. The residue was concentrated twice from toluene to remove residual water, then was triturated with methanol. A solid was isolated by filtration and was dried under vacuum to provide 0.68 g of 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride.

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Part B

Cyclohexyl isocyanate (0.285 mL, 2.20 mmol) was added to a flask containing 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride (680 mg, 1.98 mmol), triethylamine (0.311 mL, 2.2 mmol), and dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 2 hours and additional triethylamine and cyclohexyl isocyanate (1.1 equivalents each) were added. The reaction mixture was stirred overnight at room temperature, then was partitioned between dichloromethane (50 mL) and 2:1 water/saturated aqueous sodium carbonate (30 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The organic layers were combined, washed with 0.5 M aqueous sodium hydroxide (2 x 30

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mL), and concentrated under reduced pressure. The resulting white solid was triturated with ethyl acetate, isolated by filtration, and washed with ethyl acetate and water to provide 777 mg of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-*N'*-cyclohexylurea.

5

Part C

N-Hydroxyphthalimide (5.32 g, 32.6 mmol) and triethylamine (4.54 mL, 32.6 mmol) were added to a suspension of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-*N'*-cyclohexylurea (9.00 g, 23.3 mmol) in DMF (1 L). The reaction mixture was allowed to stir overnight, then was concentrated under reduced pressure to a white slurry. Methanol was added and a white solid was isolated by filtration, washed with methanol, and dried under vacuum to afford 11.6 g of *N*-cyclohexyl-*N'*-[4-(8-{{(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy}methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]urea.

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Part D

Anhydrous hydrazine (0.50 mL, 16.1 mmol) was added to a stirred suspension of *N*-cyclohexyl-*N'*-[4-(8-{{(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy}methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]urea (3.00 g, 5.36 mmol) in ethanol (36 mL). Over the next hour, dichloromethane (40 mL) and ethanol (20 mL) were added to prevent the reaction from solidifying. After one more hour, the solvent was removed under reduced pressure, then acetone (27 mL) and methanol (27 mL) were added. The mixture was stirred at room temperature for 2 hours, then a solid was isolated by filtration and washed with methanol. To the solid was added 1 M aqueous sodium hydroxide and the mixture was sonicated for 1 minute. The solid was isolated by filtration, washed with water, and dried under vacuum at 70 °C to provide 2.36 g of *N*-cyclohexyl-*N'*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy}methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}urea.

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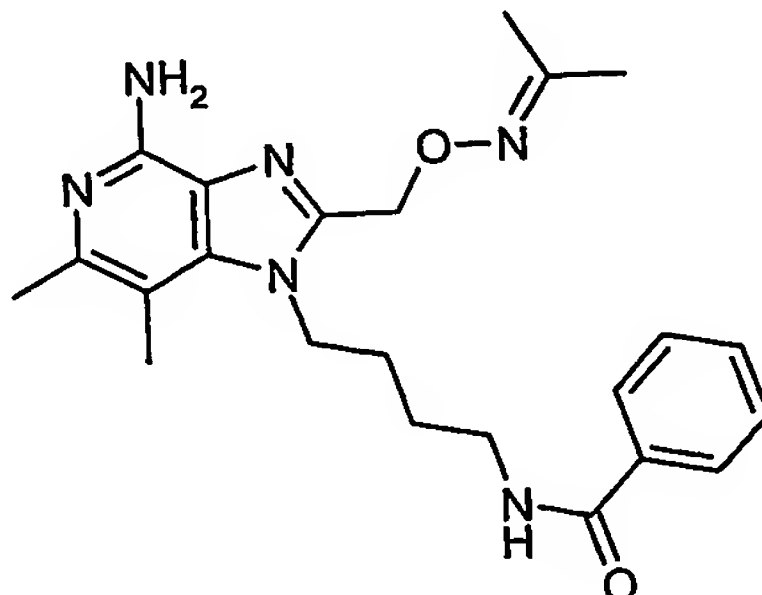
Part E

A mixture of *N*-cyclohexyl-*N'*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy}methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}urea (2.30 g, 4.90 mmol), triphenylphosphine (2.81 g, 10.7 mmol), and 1,2-dichlorobenzene (50 mL) was heated at 120 °C for 1 day. The reaction mixture was allowed to cool to room temperature and was stirred overnight. The solvent was removed under reduced pressure. The residue was triturated with methanol/ethyl acetate to afford 1.5 g of the starting material after filtration. The filtrate was concentrated under reduced pressure and the residue was combined with the 1.5 g of starting material. The combined material was resubjected to the reaction conditions for 2 days. The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure, and was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-30% CMA in chloroform) to provide the ylide product. The ylide product was dissolved in methanol/water/acetic acid and heated at 50 °C for 1 day. More acetic acid was added and the reaction was heated at 55 °C for 1 more day. The reaction was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was partitioned between saturated aqueous sodium carbonate (100 mL) and chloroform (100 mL). The aqueous layer was extracted with chloroform (3 x 40 mL). The organic layers were combined, washed with saturated aqueous sodium carbonate (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was purified by chromatography, followed by trituration with dichloromethane/ethyl acetate, followed by crystallization from 2-propanol/water to afford a solid that was treated with 1 M aqueous HCl, isolated by filtration, and dried to afford 38 mg of *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-*N'*-cyclohexylurea as a white powder, mp 210.0-212.0 °C.

Anal. Calcd for C₂₃H₃₇N₇O₂•1.0 HCl•0.2 H₂O: C, 57.12; H, 8.00; N, 20.27; Found: C, 57.42; H, 8.39; N, 20.30.

Example 89

N-{4-[4-Amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy)methyl}-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}benzamide



5 Part A

Benzoic anhydride (3.1 g, 13.8 mmol) was added to a flask containing 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride (prepared as described in Part A of Example 88, 4.30 g, 12.5 mmol), triethylamine (3.70 mL, 26.3 mmol), and dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 day and additional triethylamine (0.5 mL) and benzoic anhydride (0.8 g) were added. The reaction mixture was stirred for 6 hours at room temperature. The volatiles were removed under reduced pressure and water (50 mL) followed by ethyl acetate (50 mL) were added to the solid residue. The mixture was sonicated for 1 minute, then the solid was isolated by filtration, washed with water and ethyl acetate, and dried under vacuum to afford 4.7 g of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide.

Part B

The method described in Part C of Example 88 was used to convert 4.7 g of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide into 5.7 g of *N*-[4-(8-{{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide.

Part C

Anhydrous hydrazine (0.47 mL, 15 mmol) was added to a stirred suspension of *N*-[4-(8-{{(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy}methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]benzamide (2.8 g, 5.0 mmol) in ethanol (50 mL). After two hours, a solid was isolated by filtration and the filter cake was washed with ethanol. Acetone (25 mL) and methanol (25 mL) were added to the solid and the mixture was stirred overnight. The volatiles were removed under reduced pressure to afford a solid that was triturated with 1 M aqueous sodium hydroxide (10 mL) and 1:1 methanol/acetone (4 mL). The solid was isolated by filtration, washed with water, and dissolved in chloroform (100 mL). The solution was dried over magnesium sulfate, filtered, concentrated under reduced pressure, and dried under vacuum to afford 1.9 g of a *N*-{4-[5,6-dimethyl-8-({(1-methylethylidene)amino}oxy)methyl]-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide as a white solid.

Part D

A mixture of *N*-{4-[5,6-dimethyl-8-({(1-methylethylidene)amino}oxy)methyl]-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide (1.9 g, 4.2 mmol), triphenylphosphine (2.2 g, 8.4 mmol), and 1,2-dichlorobenzene (40 mL) was heated at 125 °C for 2 days. The reaction was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was dissolved in methanol (20 mL) and 1 M aqueous hydrochloric acid (20 mL) and heated at 40 °C for 6 hours. The reaction was allowed to stand at room temperature overnight and a white precipitate formed that was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was partitioned between 1 M aqueous hydrochloric acid (20 mL) and chloroform (10 mL). The aqueous layer was extracted with chloroform (3 x 10 mL). The organic layers were combined, washed with saturated aqueous sodium carbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The solid was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 10-35% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure. The solid was triturated with ethyl acetate and was isolated by filtration, washed with ethyl acetate, and dried under vacuum at 50 °C overnight to provide

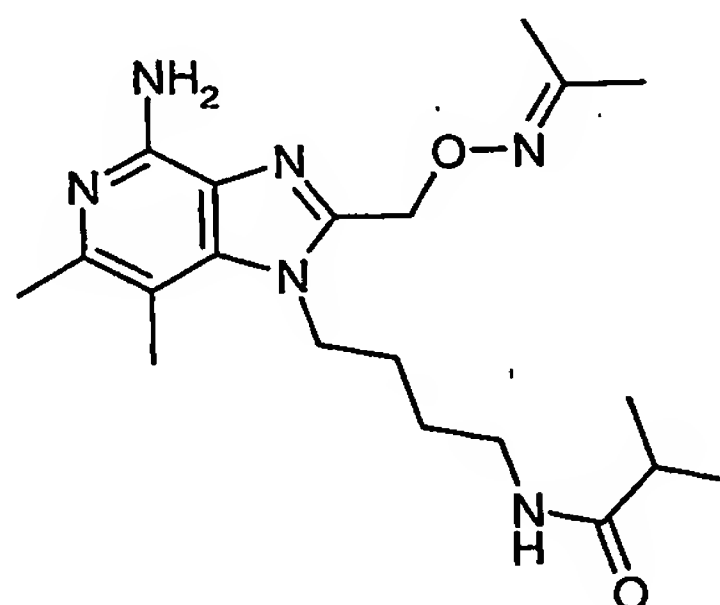
0.85 g of *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}benzamide as a white powder, mp 206.0-208.0 °C.

Anal. Calcd for C₂₃H₃₀N₆O₂•0.06 CHCl₃: C, 64.46; H, 7.05; N, 19.56; Found: C, 64.31; H, 7.06; N, 19.55.

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Example 90

N-{4-[4-Amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-2-methylpropanamide



10 Part A

Isobutyric anhydride (2.28 mL, 13.8 mmol) was added to a flask containing 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride (prepared as described in Part A of Example 88, 4.30 g, 12.5 mmol), triethylamine (3.66 mL, 26.3 mmol), and dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. The solution was concentrated under reduced pressure and water (50 mL) followed by ethyl acetate (50 mL) were added to the solid residue. The mixture was sonicated for 1 minute, then the solid was isolated by filtration, washed with water and ethyl acetate. Toluene was added to the solid and the mixture was concentrated under reduced pressure. The solid was dried under vacuum to afford 4.12 g of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide.

Part B

The general method described in Part C of Example 88 was used to convert 4.10 g *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide into 4.92 g of *N*-[4-(8-{{[(1,3-dioxo-1,3-dihydro-2*H*-

isoindol-2-yl)oxy)methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]-2-methylpropanamide.

Part C

5 Anhydrous hydrazine (0.91 mL, 29 mmol) was added to a stirred suspension of *N*-[4-(8-{{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy)methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]-2-methylpropanamide (4.90 g, 9.71 mmol) in ethanol (100 mL). Dichloromethane (50 mL) was added. After four hours, acetone (50 mL) was added and the reaction mixture was stirred overnight. A solid was removed by filtration and washed with methanol. The filtrate was concentrated to provide a solid that was triturated with 1:1 saturated aqueous sodium bicarbonate/water. The solid was isolated by filtration, washed with water, and dissolved in chloroform (300 mL). The solution was washed with water (2 x 50 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and dried under vacuum to afford *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy)methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide that was used in the next experiment.

Part D

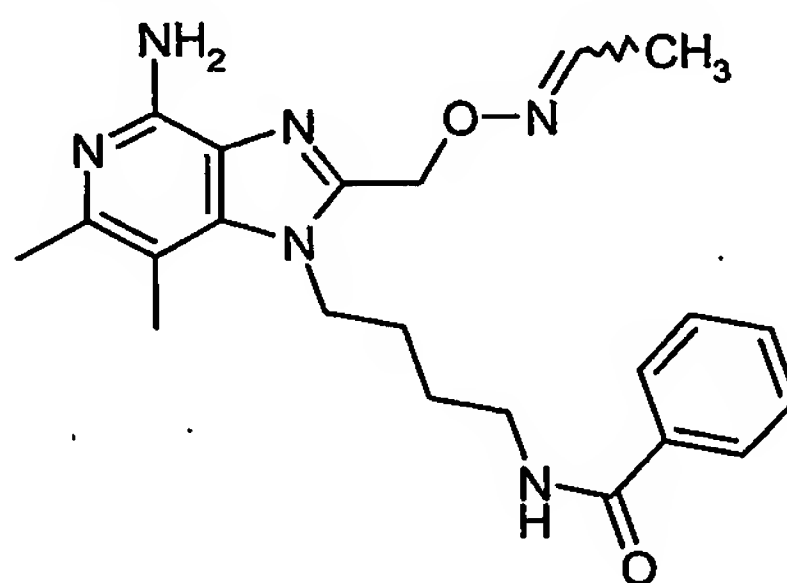
20 A mixture of *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy)methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide (from Part C, approximately 9.71 mmol), triphenylphosphine (5.1 g, 19 mmol), and 1,2-dichlorobenzene (97 mL) was heated at 125 °C for 2 days, then stirred at room temperature for 3 days, then heated at 130 °C for 5 hours. The reaction was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was dissolved in methanol (80 mL) and 1 M aqueous hydrochloric acid (40 mL) and heated at 40 °C for 6 hours. The reaction was allowed to stir at room temperature overnight and a white precipitate formed that was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was partitioned between 1 M aqueous hydrochloric acid (20 mL) and chloroform (10 mL). The aqueous layer was extracted with chloroform (3 x 10 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

The solid was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-55% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure. The resulting solid was triturated with acetonitrile and then was recrystallized from acetonitrile to provide *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy)methyl}-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-2-methylpropanamide as a white powder, mp 180.0-181.0 °C.

Anal. Calcd for C₂₀H₃₂N₆O₂: C, 61.83; H, 8.30; N, 21.63; Found: C, 61.65; H, 8.65; N, 21.70.

Example 91

N-{4-[4-Amino-2-({[ethylideneamino]oxy)methyl}-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}benzamide



Part A

Anhydrous hydrazine (0.481 mL, 15.3 mmol) was added to a stirred suspension of *N*-[4-(8-{{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide (prepared as described in Part B of Example 89, 2.86 g, 5.11 mmol) in ethanol (50 mL). The reaction was stirred overnight and then was concentrated under reduced pressure. Methanol (25 mL) was added and the mixture was cooled to 0 °C. Acetaldehyde (2.9 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was concentrated partially under reduced pressure, then 1 M aqueous sodium hydroxide (50 mL) was added and the mixture was sonicated for 1 minute. The solid was isolated by filtration, washed with water, and dried under vacuum at 70 °C to provide a 3:1 ratio of oxime isomers of *N*-{4-[8-({[ethylideneamino]oxy)methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide.

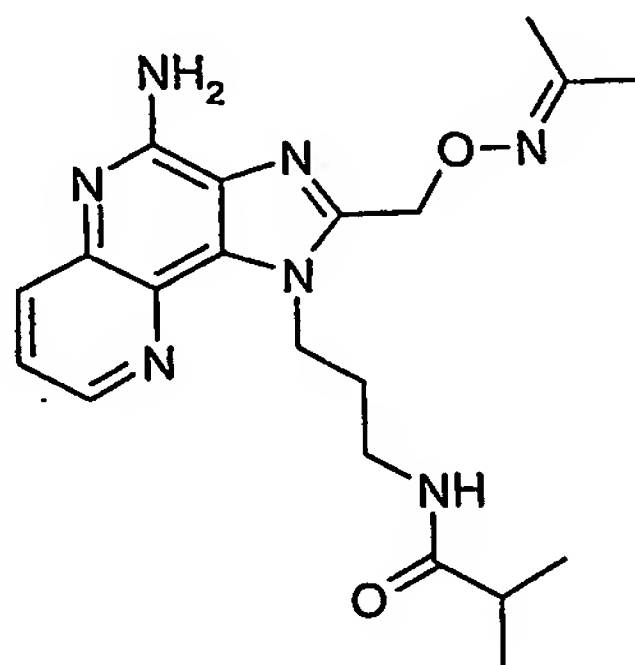
Part B

A mixture of *N*-{4-[8-({[ethylideneamino]oxy}methyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide (2.0 g, 4.6 mmol), triphenylphosphine (2.4 g, 9.2 mmol), and 1,2-dichlorobenzene (50 mL) was heated at 125 °C for 2 days. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was dissolved in methanol (40 mL) and 1 M aqueous hydrochloric acid (20 mL) was added. The mixture was heated at 50 °C for 6 hours. The mixture was allowed to stand at room temperature overnight and a white precipitate formed that was removed by filtration. The methanol was removed under reduced pressure and chloroform (20 mL) was added. The aqueous phase was adjusted to pH 12 with 1 M aqueous sodium hydroxide. The aqueous phase was extracted with chloroform (3 x 10 mL). The organic phases were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 10-35% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure to provide a solid that was triturated with acetonitrile, crystallized from acetonitrile, and purified again by chromatography as described above using 5-40% CMA in chloroform as the eluent to provide 32 mg of *N*-{4-[4-amino-2-({[ethylideneamino]oxy}methyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}benzamide as a white powder and as a mixture (approximately 1:1 mixture) of oxime isomers, mp 192.0-194.0 °C.

Anal. Calcd for C₂₂H₂₈N₆O₂•0.07 CHCl₃: C, 63.59; H, 6.79; N, 20.16; Found: C, 63.25; H, 7.03; N, 20.43.

Example 92

N-{3-[4-Amino-2-({[(1-methylethylidene)amino]oxy)methyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-2-methylpropanamide



5 Part A

A solution of *tert*-butyl 3-aminopropylcarbamate (15.7 g, 90.2 mmol) in dichloromethane (50 mL) was added dropwise over 30 minutes to a solution of 4-chloro-3-nitro[1,5]naphthyridine (18.0 g, 85.9 mmol) and triethylamine (15.6 mL, 112 mmol) in dichloromethane (235 mL) at room temperature. The reaction mixture was stirred for 2.5
10 hours and then concentrated under reduced pressure to afford an orange solid. Water (300 mL) was added and the mixture was stirred for 1 hour. The solid was isolated by filtration, washed with water (3 x 50 mL), and dried under vacuum at 70 °C to afford 29.5 g of *tert*-butyl 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propylcarbamate as a yellow solid.

15 Part B

A mixture of *tert*-butyl 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propylcarbamate (20.0 g, 57.6 mmol), 5% platinum on carbon, and ethyl acetate was hydrogenated on a Parr apparatus for 2 hours at 30 psi (2.1×10^5 Pa). The mixture was filtered through CELITE filter agent, which was rinsed afterwards with ethyl acetate (150 mL). The filtrate was
20 concentrated to afford *tert*-butyl 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propylcarbamate as a yellow foam, all of which was used in the next step.

Part C

Chloroacetyl chloride (5.00 mL, 63.4 mmol) was added dropwise to a 0 °C solution
25 of *tert*-butyl 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propylcarbamate (from Part B,

approximately 57.6 mmol) in dichloromethane (230 mL). The reaction was allowed to warm to room temperature and was stirred for 1 hour. The solvent was removed under reduced pressure to afford *tert*-butyl 3-({3-[(chloroacetyl)amino]-[1,5]naphthyridin-4-yl} amino)propylcarbamate hydrochloride as a solid, all of which was used in the next step.

5

Part D

To a solution of *tert*-butyl 3-({3-[(chloroacetyl)amino][1,5]naphthyridin-4-yl} amino)propylcarbamate hydrochloride (from Part C, approximately 57.6 mmol) in 3:1 ethanol/water (240 mL) was added 6 M aqueous potassium carbonate. The reaction mixture was stirred at room temperature for 1 hour, 40 °C for 1.5 hour, then at room temperature overnight. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane (250 mL) and water (150 mL). The aqueous layer was extracted with dichloromethane (2 x 75 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 18.9 g of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propylcarbamate.

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Part E

Concentrated hydrochloric acid (15 mL) was added to a suspension of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propylcarbamate (8.0 g, 21.3 mmol) in methanol (90 mL). The resulting solution was allowed to stir at room temperature for 72 hours. A solid formed that was isolated by filtration, washed with a minimal amount of methanol, and dried under vacuum to afford 6.11 g of 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-amine hydrochloride as a pale yellow solid.

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Part F

iso-Butyric anhydride (0.850 mL, 5.11 mmol) and triethylamine (1.50 mL, 10.7 mmol) were added to a suspension of 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-amine hydrochloride (1.33 g, 4.26 mmol) in dichloromethane (25 mL). The reaction mixture was stirred for 3 hours and the suspension

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slowly dissolved. The solution was partitioned between dichloromethane (20 mL) and saturated aqueous sodium bicarbonate (30 mL). The aqueous layer was extracted with dichloromethane (20 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford 1.41 g of *N*-{3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-2-methylpropanamide, which was used without further purification.

Part G

mCPBA (0.985 g, 5.71 mmol) was added to a suspension of *N*-{3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-2-methylpropanamide (1.41 g, 4.08 mmol) in chloroform (20 mL). The reaction mixture was allowed to stir for 4 hours at room temperature. Concentrated ammonium hydroxide (5 mL) followed by *p*-toluenesulfonyl chloride (0.854 g, 4.48 mmol) were added and the mixture was stirred at room temperature for 1 hour. The mixture was diluted with chloroform (25 mL) and brine (40 mL) and transferred to a separatory funnel. The aqueous layer was extracted with chloroform (20 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford a tan solid. Trituration with methanol and isolation by filtration afforded 0.670 g of *N*-{3-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-2-methylpropanamide.

Part H

Triethylamine (0.340 mL, 2.41 mmol) and *N*-hydroxyphthalimide (0.333 g, 2.04 mmol) were added to a suspension of *N*-{3-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-2-methylpropanamide (0.670 g, 1.86 mmol) in DMF (10 mL). The reaction was allowed to stir at room temperature for 4 hours, then was concentrated under reduced pressure. The residue was triturated with methanol to afford 0.848 g of *N*-[3-(4-amino-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl]-2-methylpropanamide as a tan solid.

Part I

Anhydrous hydrazine (0.160 mL, 5.22 mmol) was added to a suspension of *N*-[3-(4-amino-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl)-1*H*-imidazo[4,5-*c*]-[1,5]naphthyridin-1-yl)propyl]-2-methylpropanamide (0.848 g, 1.74 mmol) in ethanol (10 mL). The mixture was allowed to stir at room temperature for 2.5 hours, then was concentrated under reduced pressure to yield crude *N*-(3-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propyl)-2-methylpropanamide as a yellow solid, all of which was used in the next step.

10 Part J

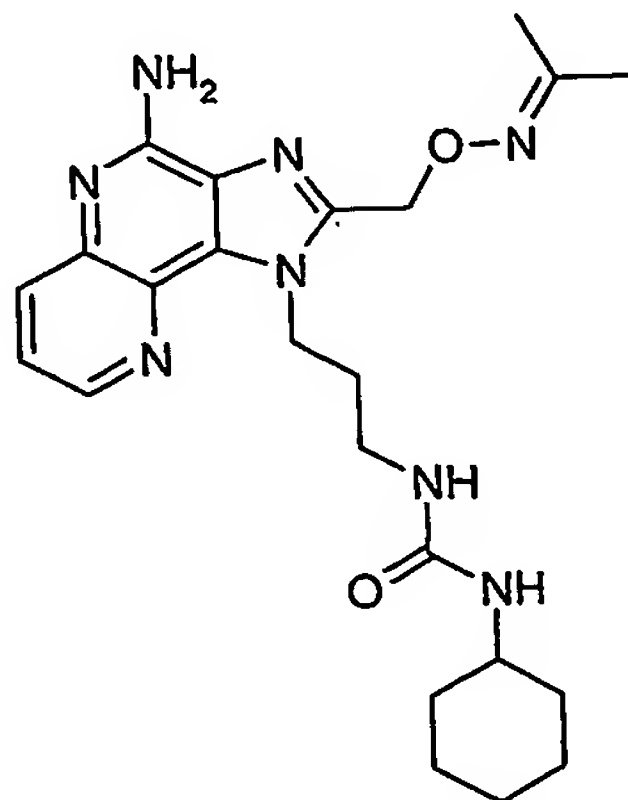
Acetone (1 mL) was added to a solution of the *N*-(3-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propyl)-2-methylpropanamide from Part I in methanol (10 mL). The reaction mixture was allowed to stir overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by chromatography on a HORIZON HPFC system (silica gel, 0-25% CMA in chloroform) to afford 0.495 g of *N*-{3-[4-amino-2-[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propyl}-2-methylpropanamide as off-white needles, mp 195-197 °C.

MS (APCI) *m/z* 398 (*M* + *H*)⁺;

20 Anal. calcd for C₂₀H₂₇N₇O₂: C, 60.44; H, 6.85; N, 24.67. Found: C, 60.28; H, 7.14; N, 24.34.

Example 93

N-{3-[4-Amino-2-({[(1-methylethylidene)amino]oxy)methyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea



5 Part A

Cyclohexyl isocyanate (0.70 mL, 5.50 mmol) and triethylamine (1.74 mL, 12.5 mmol) were added to a stirred suspension of 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-amine hydrochloride (prepared as described in Parts A-E of Example 92, 1.56 g, 5.00 mmol) in dichloromethane (25 mL). A solution eventually
 10 formed from which a solid precipitated. The mixture was allowed to stand at room temperature overnight, then the solid was isolated by filtration and washed with a minimal amount of dichloromethane to afford 1.52 g of *N*-{3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea as a white solid.

15 Part B

mCPBA (0.982 g, 5.69 mmol) was added to a suspension of *N*-{3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea (1.52 g, 3.79 mmol) in chloroform (20 mL). The reaction mixture was allowed to stir for 4 hours, then additional mCPBA (1 equivalent) was added. After 2 hours, the reaction
 20 mixture was diluted with chloroform and washed with saturated aqueous sodium bicarbonate (2 x 40 mL). The aqueous layers were combined and back-extracted with chloroform (20 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford 1.61 g of a pale yellow solid. The solid was suspended in chloroform (20 mL) and concentrated ammonium hydroxide (5 mL) and *p*-

toluenesulfonyl chloride (0.795 g, 4.17 mmol) were added. The reaction mixture was allowed to stir at room temperature for 2 hours, then the product was isolated by filtration to afford 0.972 g of *N*-{3-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea as a white solid.

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Part C

The general method described in Part H of Example 92 was used to convert *N*-{3-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea (0.972 g, 2.34 mmol) into 0.738 g of *N*-[3-(4-amino-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propyl]-*N'*-cyclohexylurea, which was isolated as a white solid.

10

Part D

The general method described in Part I of Example 92 was used to convert *N*-[3-(4-amino-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propyl]-*N'*-cyclohexylurea (0.738 g, 1.36 mmol) into 0.561 g of *N*-(3-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propyl)-*N'*-cyclohexylurea, which was isolated as a white solid and used without purification in the next step.

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Part E

A modification on the general method described in Part J of Example 92 was used to convert *N*-(3-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propyl)-*N'*-cyclohexylurea (from Part D, approximately 1.36 mmol) into 0.403 g of *N*-{3-[4-amino-2-([(1-methylethylidene)amino]oxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, 0-30% CMA in chloroform). *N*-{3-[4-amino-2-([(1-methylethylidene)amino]oxy)methyl]-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propyl}-*N'*-cyclohexylurea was isolated as white needles, mp 207-208 °C.

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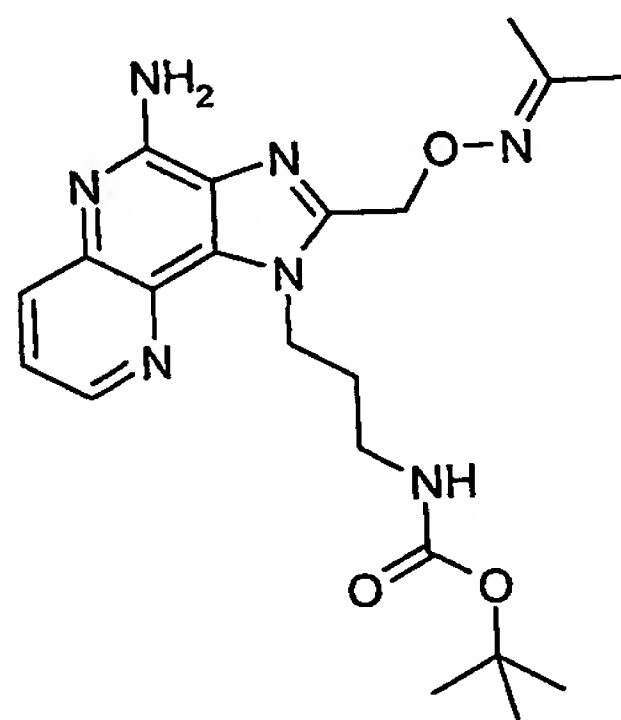
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MS (APCI) *m/z* 453 (*M* + *H*)⁺;

Anal. calcd for $C_{23}H_{32}N_8O_2$: C, 61.04; H, 7.13; N, 24.76. Found: C, 60.98; H, 7.27; N, 24.80.

Example 94

5 *tert*-Butyl 3-[4-amino-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propylcarbamate



Part A

10 *N*-Hydroxyphthalimide (2.06 g, 12.7 mmol) and triethylamine (2.40 mL, 17.3 mmol) were added to a solution of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propylcarbamate (prepared as described in Parts A-D of Example 92, 11.5 mmol) in DMF (60 mL). The reaction was allowed to stir overnight at room temperature. The resulting orange suspension was diluted with water (40 mL) and the solid was isolated by filtration, washed with water (2 x 30 mL), and dried in a vacuum oven at 70 °C to afford 4.86 g of *tert*-butyl 3-(2-{{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propylcarbamate as a white solid. The material was used without further purification in the next step.

Part B

20 mCPBA (2.33 g, 13.5 mmol) was added to a suspension of *tert*-butyl 3-(2-{{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propylcarbamate (4.86 g, 9.67 mmol) in chloroform (50 mL). The reaction mixture was allowed to stir for 4 hours, then concentrated ammonium hydroxide (27 mL) and *p*-toluenesulfonyl chloride (2.03 g, 10.6 mmol) were added. The reaction mixture was 25 allowed to stir overnight at room temperature, then was filtered. The filtrate was diluted

with saturated aqueous sodium bicarbonate (50 mL) and extracted with chloroform (2 x 40 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford a brown solid that was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform) to afford 1.00 g of *tert*-butyl 3-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propylcarbamate as a yellow solid that contained some minor impurities.

Part C

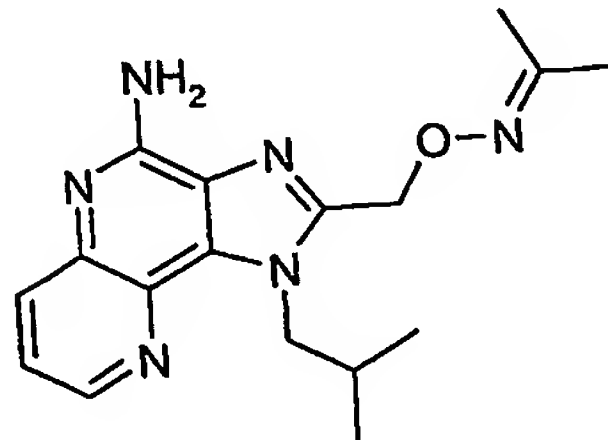
A modification on the general method described in Part J of Example 92 was used to convert *tert*-butyl 3-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}propylcarbamate (1.00 g, 2.58 mmol) into 1.11 g of crude *tert*-butyl 3-[4-amino-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propylcarbamate. Some of the product (0.709 g) was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25 % CMA in chloroform) to afford 0.271 g of *tert*-butyl 3-[4-amino-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propylcarbamate as off-white needles, mp 148-150 °C.

MS (APCI) m/z 428 ($M + H$)⁺;

Anal. calcd for C₂₁H₂₉N₇O₃: C, 59.00; H, 6.84; N, 22.93. Found: C, 58.69; H, 6.86; N, 22.80.

Example 95

Acetone *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-2-yl)methyl} oxime



5 Part A

Isobutylamine (15.6 mL, 157 mmol) was added dropwise to a 5 °C solution of 4-chloro-3-nitro[1,5]naphthyridine (15.0 g, 71.6 mmol) in dichloromethane (300 mL). The reaction was allowed to stir at room temperature for 4 hours, then was concentrated under reduced pressure to afford a residue that was treated with water (300 mL). The mixture was stirred for 30 minutes, then a solid was isolated by filtration, rinsed with water (100 mL), and dried in a vacuum oven at 50 °C overnight to afford 17.25 g of *N*-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine as a yellow solid.

15 Part B

The general method described in Part B of Example 92 was used to convert *N*-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (17.25 g, 70.0 mmol) into *N*⁴-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine, which was isolated as a thick, yellow oil and used directly in the next step without purification.

20 Part C

The general method described in Part C of Example 92 was used to convert *N*⁴-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine (from Part B) into 2-chloro-*N*-{4-[(2-methylpropyl)amino][1,5]naphthyridin-3-yl}acetamide hydrochloride, which was isolated as a pale yellow solid that was used directly in the next step without purification.

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Part D

To a solution of 2-chloro-*N*-{4-[(2-methylpropyl)amino][1,5]naphthyridin-3-yl}acetamide hydrochloride (from Part C, approximately 70 mmol) in 3:1 ethanol/water (280 mL) was added 6 M aqueous potassium carbonate (17.5 mL). The reaction mixture was stirred at room temperature over the weekend. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane (200 mL) and brine (100 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 19.5 g of 2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine, which contained a small amount of dichloromethane and was used without further purification in the next step.

Part E

mCPBA (70% pure, 9.85 g, 40.0 mmol) was added to a solution of 2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (5.49 g, 20.0 mmol) in chloroform (80 mL). The reaction mixture was allowed to stir for 1.5 hours, then was diluted with dichloromethane (150 mL) and washed with saturated aqueous sodium bicarbonate (2 x 75 mL). The aqueous layers were combined and back-extracted with dichloromethane (2 x 30 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford a yellow semi-solid that was used immediately without purification in the next step.

Part F

The material from Part E was dissolved in methanol (70 mL) and the solution was cooled to 0 °C. Concentrated ammonium hydroxide (6.7 mL) was added, followed by dropwise addition of benzenesulfonyl chloride (5.25 mL, 42.0 mmol). The reaction mixture was stirred at 0 °C for 1 hour. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane (150 mL) and saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with dichloromethane (50 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by chromatography using a HORIZON

HPFC system (silica gel, gradient elution with 0-25 % CMA in chloroform) to afford 4.14 g of approximately 85% pure 2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, which was used in the next step without further purification.

5 Part G

The general method described in Part H of Example 92 was used to convert the material from Part F (85% pure, 4.14 g, 14.3 mmol) into 2.81 g of 2-[(4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl)methoxy]-1*H*-isoindole-1,3(2*H*)-dione.

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Part H

Anhydrous hydrazine (0.640 mL, 20.2 mmol) was added to a suspension of 2-[(4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl)methoxy]-1*H*-isoindole-1,3(2*H*)-dione (2.81 g, 6.75 mmol) in ethanol (40 mL). Gradually, a solution formed from which a solid began to precipitate. The reaction mixture was stirred overnight at room temperature, then was concentrated under reduced pressure. The residue was triturated with 1 M aqueous hydrochloric acid (50 mL). The mixture was sonicated and the solid was isolated by filtration. The filtrate was adjusted to pH 8 with solid sodium carbonate and extracted with dichloromethane (3 x 25 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford a yellow solid. The solid was triturated with methanol to afford 0.863 g of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a white solid.

25 Part I

The general method described in Part J of Example 92 was used to convert 2-[(aminooxy)methyl]-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.555 g, 1.94 mmol) into acetone *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl} oxime. The crude product was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform) followed by crystallization from methanol to afford 0.262 g of

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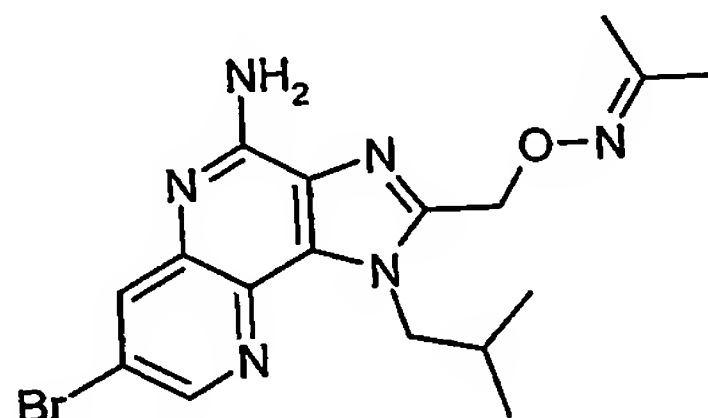
acetone *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl}oxime as yellow crystals that were dried in a vacuum oven overnight at 85 °C, mp 173-175 °C.

MS (ESI) m/z 327 ($M + H$)⁺;

5 Anal. calcd for C₁₇H₂₂N₆O: C, 62.56; H, 6.79; N, 25.75. Found: C, 62.49; H, 7.08; N, 26.01.

Example 96

10 Acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-2-yl]methyl}oxime



Part A

15 Isobutylamine (16.2 mL, 163 mmol) was added dropwise to a 0 °C solution of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (approximately 74.1 mmol) in dichloromethane (350 mL). The reaction mixture was allowed to stir and warm to room temperature for 3 hours, then was diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (300 mL). The aqueous layer was back-extracted with dichloromethane (2 x 75 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford 23.06 g of 7-bromo-*N*-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine as a yellow solid.

Part B

25 The general method described in Part B of Example 92 was used to convert 7-bromo-*N*-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (23.06 g, 70.9 mmol) into 7-bromo-*N*⁴-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine. The mixture was hydrogenated at 40 psi (2.8 x 10⁵ Pa) for 2.5 hours, then worked up as described in Part B of Example 92.

Part C

The general method described in Part C of Example 92 was used to convert the material from Part B into *N*-{7-bromo-4-[(2-methylpropyl)amino][1,5]naphthyridin-3-yl}-2-chloroacetamide hydrochloride, which was all used in the next step.

5

Part D

The material from Part C (approximately 70.9 mmol) was suspended in 3:1 ethanol/water (280 mL) and 6 M aqueous potassium carbonate (17.7 mL, 106 mmol) was added. After 30 minutes, the mixture had solidified, additional ethanol was added, and stirring was resumed. The reaction mixture was stirred overnight at room temperature. Additional 6 M aqueous potassium carbonate (18 mL) was added and stirring was continued for another 2 days. The reaction mixture was concentrated under reduced pressure, the residue was partitioned between dichloromethane (200 mL) and water (100 mL), and the mixture was adjusted to pH 8 with 2 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (2 x 35 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to yield 22.8 g of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a tan solid.

10

15

20 Part E

mCPBA (70% pure, 11.2 g, 45.2 mmol) was added to a solution of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (8.00 g, 22.6 mmol) in chloroform (100 mL). The reaction mixture was allowed to stir for 3 hours, then was diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (250 mL). The aqueous layers were combined and back-extracted with dichloromethane (2 x 30 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford an oily solid that was used immediately without purification in the next step.

25

Part F

The material from Part E was dissolved in methanol (100 mL) and the solution was cooled to 0 °C. Concentrated ammonium hydroxide (7.5 mL) was added, followed by dropwise addition of benzenesulfonyl chloride (6.10 mL, 47.5 mmol). The reaction mixture was stirred at 0 °C for 1 hour. The volatiles were removed under reduced pressure and the solid was triturated with dichloromethane. A tan solid (4.92 g) was isolated by filtration. The filtrate was concentrated and the resulting solid was triturated with acetonitrile. A tan solid (3.62 g) was isolated by filtration. The two batches of tan solid were combined and used without further purification in the next step.

Part G

The material from Part F was dissolved in DMF and *N*-hydroxyphthalimide (2.12 g, 13.0 mmol) and triethylamine (2.1 mL, 15.3 mmol) were added. The red solution was stirred at room temperature overnight, then the solvent was removed under reduced pressure. The residue was triturated with methanol and a tan solid was isolated by filtration to afford 4.23 g of 2-{{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione, which was used without further purification in the next step.

Part H

Anhydrous hydrazine (0.80 mL, 25.6 mmol) was added to a suspension of 2-{{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione (4.23 g, 8.54 mmol) in ethanol (45 mL). The reaction mixture was stirred overnight at room temperature, then was concentrated under reduced pressure. The residue was triturated with 1 M aqueous hydrochloric acid (50 mL). A tan solid was isolated by filtration and was carried on to the next step.

Part I

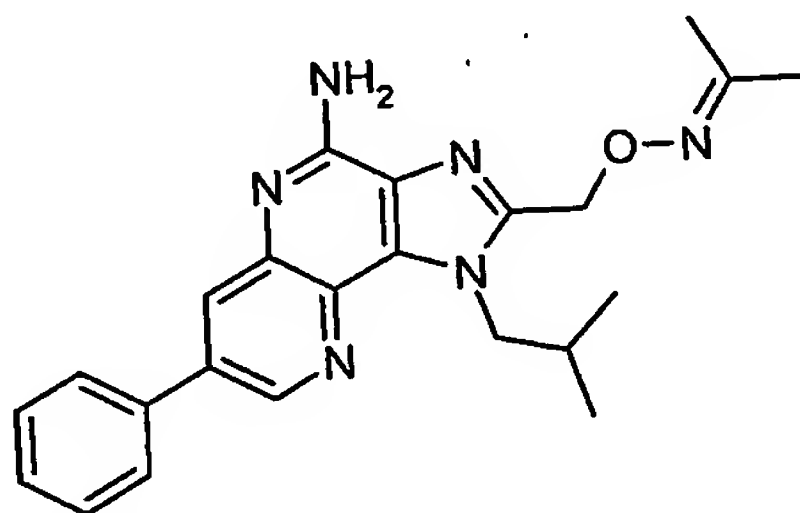
Acetone (10 mL) was added to a suspension of the material from Part H in methanol (80 mL). The reaction mixture was allowed to stir overnight at room temperature. The volatiles were removed under reduced pressure and the residue was

triturated with dichloromethane. A solid was isolated by filtration and was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution 0-30% CMA in chloroform) to afford a thick oil that was crystallized from acetonitrile. The crystals isolated by filtration, then were partitioned between chloroform and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crystalline solid was triturated with acetonitrile, isolated by filtration, and dried under vacuum at 120 °C to afford 1.27 g of acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl} oxime as off-white needles, mp 176.5-177.5 °C.

MS (ESI) m/z 406 ($M + H$)⁺;
 Anal. calcd for C₁₇H₂₁BrN₆O: C, 50.38; H, 5.22; N, 20.74. Found: C, 50.29; H, 5.24; N, 20.95.

Example 97

Acetone *O*-{[4-amino-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-2-yl]methyl} oxime

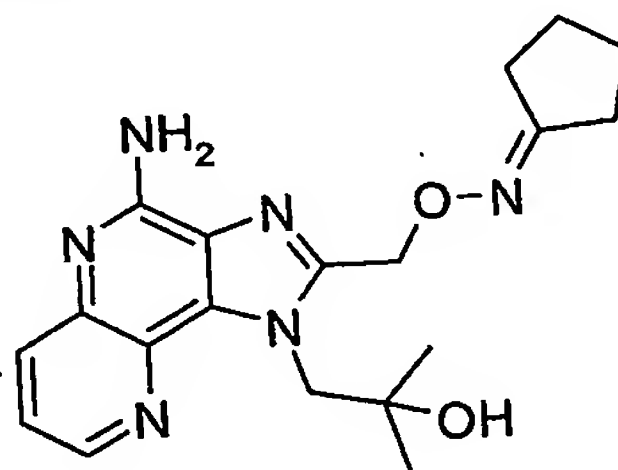


A flask containing mixture of acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl} oxime (prepared as described in Example 96, 1.16 g, 2.86 mmol), phenylboronic acid (0.42 g, 3.43 mmol), triphenylphosphine (7 mg, 0.026 mmol), 2 M aqueous sodium carbonate (4.3 mL, 8.58 mmol), and 5:1 propanol/water (18 mL) was evacuated under reduced pressure and back-filled with nitrogen gas. Palladium(II) acetate (2 mg, 0.009 mmol) was added, and the flask was again evacuated and back-filled with nitrogen gas. The reaction mixture was heated at 100 °C for 18 hours. The reaction mixture was allowed to cool to room temperature and was diluted with dichloromethane (40 mL) and water (30 mL). The aqueous layer was extracted with dichloromethane (2 x 15 mL). The organic layers were

combined, dried over magnesium sulfate, filtered, and concentrated to afford a tan solid. The solid was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform) to afford a thick oil that was crystallized from acetonitrile. The crystals were isolated by filtration and dried at 80 °C in a vacuum oven to yield 0.501 g of acetone *O*-{[4-amino-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl}oxime as a white powder, mp 196-197 °C. MS (ESI) *m/z* 403 (*M* + *H*)⁺; Anal. calcd for C₂₃H₂₆N₆O: C, 68.63; H, 6.51; N, 20.88. Found: C, 68.56; H, 6.62; N, 21.04.

Example 98

Cyclopentanone *O*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl}oxime



Part A

1-Amino-2-methyl-propan-2-ol (42.1 g, 0.472 mol) was added slowly to a solution of 4-chloro-3-nitro[1,5]naphthyridine (99.0 g, 0.472 mol) and triethylamine (132 mL, 0.945 mol) in chloroform (1.98 L) at room temperature. The reaction mixture was stirred for 45 minutes. The reaction mixture, which contained a precipitate, was divided in half. Each half was washed with saturated aqueous sodium bicarbonate (750 mL). The precipitate was isolated from the aqueous phases by filtration and dried overnight under vacuum. The organic phases were concentrated under reduced pressure. The residue was triturated with hot 2-propanol and then filtered to yield short yellow needles. The crystals were combined with the solid that was isolated above, and all the material was carried on without further manipulation to the next step.

Part B

The material from Part A was dissolved in 2-propanol (490 mL) and acetonitrile (1.63 L). To the solution was added 5% platinum on carbon (6.5 g). The mixture was hydrogenated overnight on a Parr apparatus, then was filtered through CELITE filter agent. The filtrate was concentrated under reduced pressure and the residue was used directly in the next step.

Part C

Chloroacetyl chloride (32.2 mL, 0.404 mol) was added dropwise to a solution of the material from Part B in chloroform (2.8 L). The reaction mixture was allowed to stir at room temperature. Over the next 3 hours additional chloroacetyl chloride (9.9 mL, 0.125 mol) was added and a precipitate formed. The precipitate was isolated by filtration and washed with chloroform. The solid was triturated with acetone, isolated by filtration, and dried. The solid was divided into 2 portions. To each portion was added ethanol (3.7 L) and triethylamine (65 mL). The resulting solutions were stirred at room temperature for one week, then were set aside for a week. The solutions were concentrated under reduced pressure to afford solids that were triturated with acetonitrile, isolated by filtration, dried under vacuum, and combined to afford 91.1 g of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol.

Part D

Triethylamine (4.00 mL, 28.9 mmol) and *N*-hydroxyphthalimide (2.36 g, 14.4 mmol) were added to a solution of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (4.00 g, 13.8 mmol) in DMF (80 mL). The reaction mixture was allowed to stir at room temperature for 20 minutes, during which time a precipitate formed. The precipitate was isolated by filtration and used without further purification in the next step.

Part E

Anhydrous hydrazine (1.74 mL, 55.0 mmol) was added to a stirred suspension of the material from Part D in chloroform (115 mL) at room temperature. After 15 minutes,

the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and used without purification in the next step.

Part F

5 Cyclopentanone (0.62 mL, 7.1 mmol) was added to a stirred solution of the material from Part E in methanol (40 mL). After 20 minutes, the volatiles were removed under reduced pressure and the residue (1.8 g) was used in the next step.

Part G

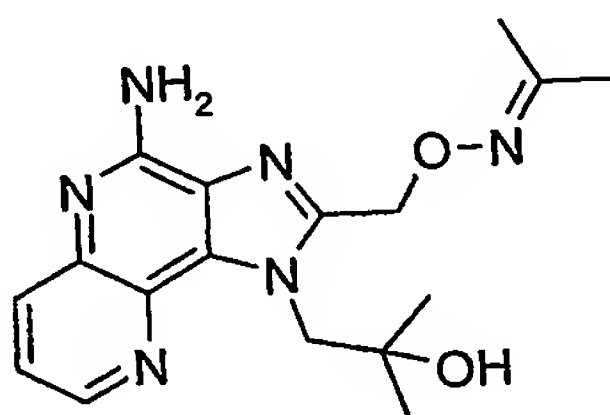
10 The residue from Part F was dissolved in chloroform (36 mL). mCPBA (a total of 9.6 g, 28.0 mmol) was added in portions to the stirred solution over the next two hours. Concentrated ammonium hydroxide (18 mL) was added, followed by chloroform (30 mL), *p*-toluenesulfonyl chloride (1.94 g, 10.2 mmol), and chloroform (100 mL). The reaction mixture was allowed to stir overnight, then was filtered. To the stirred filtrate was added
15 chloroform (400 mL), concentrated ammonium hydroxide (10 mL), and *p*-toluenesulfonyl chloride (1.94 g). After 1 hour, the reaction mixture was transferred to a separatory funnel and the aqueous phase was removed. Anhydrous ammonia was bubbled through the organic phase for 30 minutes. Additional *p*-toluenesulfonyl chloride (1.94 g) were added. Anhydrous ammonia was bubbled through the organic phase for an additional 2 hours.
20 More *p*-toluenesulfonyl chloride (1.94 g) and concentrated ammonium hydroxide (40 mL) were added, and the mixture was allowed to stir over the weekend. The mixture was transferred to a separatory funnel. The organic phase was isolated and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, elution with 2.5% methanol in chloroform) followed by chromatography using a HORIZON
25 HPFC system (silica gel, 0-20% CMA in chloroform). The product was triturated with diethyl ether, isolated by filtration, and dried in a vacuum oven to yield 10 mg of cyclopentanone *O*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-
c][1,5]naphthyridin-2-yl]methyl} oxime as a white solid, mp 195-197 °C.
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 4.4 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.44
30 (dd, *J* = 8.7 Hz, 1H), 6.90 (s, 2H), 5.46 (br s, 2H), 5.01 (s, 1H), 3.31 (s, 2H), 2.32 (t, *J* = 6.2 Hz, 2H), 2.23 (t, *J* = 6.2 Hz, 2H), 1.64 (m, 4H), 1.11 (br s, 6H);

MS (APCI) m/z 369 ($M + H$)⁺;

Anal. calcd for C₁₉H₂₄N₆O₂: C, 61.94; H, 6.57; N, 22.81. Found: C, 61.65; H, 6.40; N, 22.75.

Example 99

Acetone *O*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl} oxime



Part A

mCPBA (23.7 g, 68.8 mmol) was added to a suspension of the crude material from Part D of Example 98 (14.36 g, approximately 34.4 mmol) in chloroform (360 mL). The solution was stirred for 1 hour, then was transferred to a separatory funnel and washed with saturated aqueous sodium bicarbonate (150 mL). The organic phase was isolated and concentrated ammonium hydroxide (80 mL) followed by *p*-toluenesulfonyl chloride (6.88 g, 1.05 equivalents) was added. After 30 minutes, additional *p*-toluenesulfonyl chloride (13.8 g) was added and the mixture was allowed to stir overnight. The reaction mixture was diluted with chloroform (125 mL) and transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate (250 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, eluted with 4.25% methanol in chloroform) to afford 1.31 g of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol as a yellow solid.

Part B

Methanol (21 mL) and acetone (2.6 mL) were added to 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol (1.31 g, 4.3 mmol). The reaction was stirred for 15 minutes then concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, eluted with

0.7% methanol in chloroform) followed by recrystallization from acetonitrile/water to yield 0.56 g of acetone *O*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]-

1,5-naphthyridin-2-yl]methyl} oxime as a white solid, mp 198-200 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.49 (d, *J* = 4.4 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.44 (dd, *J* = 8.7 Hz, 1H), 6.91 (s, 2H), 5.46 (br s, 2H), 5.02 (s, 1H), 3.32 (s, 2H), 1.78 (d, *J* = 8.7 Hz, 6H), 1.12 (br s, 6H);

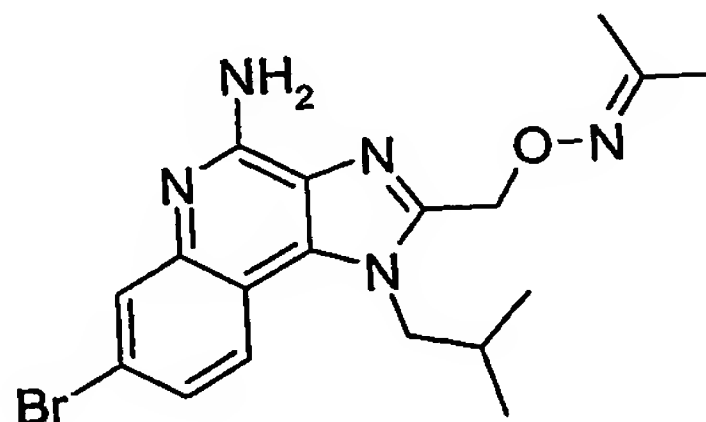
MS (APCI) *m/z* 343 (*M* + *H*)⁺;

Anal. calcd for C₁₇H₂₂N₆O₂: C, 59.63; H, 6.48; N, 24.54. Found: C, 59.42; H, 6.69; N, 24.62.

10

Example 100

Acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime



Part A

A mixture of triethyl orthoformate (154 g, 1.04 mol) and Meldrum's acid (142 g, 0.983 mol) was heated to 55°C for 4 hours. After cooling to 50 °C, a solution of 3-bromoaniline (162.6 g, 0.945 mol) in ethanol (300 mL) was added such that the temperature of the reaction was maintained between 50-55 °C. After half of the 3-bromoaniline had been added, stirring became difficult due to the formation of solids, so more ethanol (1 L) was added to facilitate stirring. Upon complete addition, the reaction was cooled to room temperature, and the solids were collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless, and the product was dried at 65 °C under vacuum to afford 287 g of 5-[(3-bromophenylimino)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione as an off-white solid.

¹H NMR (300 MHz, CDCl₃) δ 11.19 (brd, *J* = 12.8 Hz, 1H), 8.60 (d, *J* = 14.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1H), 1.75 (s, 6H).

Part B

7-Bromoquinolin-4-ol was prepared in accordance with the literature procedure (D. Dibyendu et al., *J. Med. Chem.*, 41, 4918-4926 (1998)) or by thermolysis of 5-[(3-bromophenylimino)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione in DOWTHERM A heat transfer fluid and had the following spectral properties:

¹H NMR (300 MHz, d₆-DMSO) δ 11.70 (brs, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.44 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.05 (d, *J* = 7.5 Hz, 1H).

Part C

A stirred suspension of 7-bromoquinolin-4-ol (162 g, 0.723 mol) in propionic acid (1500 mL) was brought to 110 °C. Nitric acid (85 g of 70%) was added dropwise over 1 hour such that the temperature was maintained between 110-115 °C. After half of the nitric acid had been added, stirring became difficult due to the formation of solids and an additional 200 mL of propionic acid was added. Upon complete addition, the reaction was stirred for 1 hour at 110°C, cooled to room temperature, and the solid was collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless (800 mL), and the product was dried at 60 °C under vacuum to afford 152 g of 7-bromo-3-nitro-quinolin-4-ol as a pale yellow solid.

¹H NMR (300 MHz, d₆-DMSO) δ 13.0 (brs, 1H), 9.22 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.9 Hz, 1H).

Part D

7-Bromo-3-nitroquinolin-4-ol (42 g, 156 mmol) was suspended in POCl₃ (130 mL) and brought to 102 °C under an atmosphere of N₂. After 45 min, all of the solids had dissolved, so the reaction was cooled to room temperature. The resulting solids were collected by filtration, washed with H₂O, and then partitioned with CH₂Cl₂ (3 L) and 2M Na₂CO₃ (500 mL). The organic layer was separated, washed with H₂O (1x), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 33.7 g of 7-bromo-4-chloro-3-nitroquinoline as a beige solid.

¹H NMR (300 MHz, CDCl₃) δ 9.26 (s, 1H), 8.41 (d, *J* = 1.8 Hz, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 7.90 (dd, *J* = 8.9, 2.1 Hz, 1H).

Part E

To a suspension of 7-bromo-4-chloro-3-nitroquinoline (25.0 g, 87.0 mmol) in DMF (70 mL) was added triethylamine (18.2 mL, 130 mmol). A solution of *iso*-butylamine (9.50 mL, 95.7 mmol) in DMF (20 mL) was added dropwise. The viscous reaction mixture was stirred overnight at ambient temperature. Water (200 mL) was added and the mixture was stirred for 1 hour. A solid was isolated by filtration, washed with water, and dried in a vacuum oven overnight to yield 26.1 g of 7-bromo-*N*-(2-methylpropyl)-3-nitroquinolin-4-amine as a yellow powder.

Part F

A mixture of 7-bromo-*N*-(2-methylpropyl)-3-nitroquinolin-4-amine (25.1 g, 77.4 mmol) and 5% platinum on carbon (2.5 g), dichloroethane (160 mL), and ethanol (80 mL) was hydrogenated on a Parr apparatus at 30 psi (2.1×10^5 Pa) for 2 hours. The mixture was filtered through CELITE filter agent and the filtrate was concentrated under reduced pressure to yield 23.1 g of a brown oil.

Part G

To a stirred solution of the material from Part F (23.1 g) and triethylamine (16.4 mL, 118 mmol) in dichloromethane (300 mL) was added dropwise chloroacetyl chloride (6.9 mL, 86.3 mmol). The reaction mixture was allowed to stir at room temperature for 7 days, then was concentrated under reduced pressure. The resulting brown foam was partitioned between ethyl acetate (400 mL) and 1:1 saturated aqueous sodium bicarbonate/water (400 mL). The water layer was extracted with dichloromethane (2 x 200 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was divided into three portions, which were purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with ethyl acetate in hexanes). The purified material was combined to yield 18.32 g of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a yellow solid.

Part H

To a solution of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (13.9 g, 39.4 mmol) in chloroform (300 mL) at room temperature was added mCPBA (77% pure, 17.7 g, 78.8 mmol) over ten minutes. The reaction mixture was stirred at room temperature for 3 hours, then concentrated ammonium hydroxide (150 mL) was added, followed by *p*-toluenesulfonyl chloride (9.00 g, 47.3 mmol, added in portions over 10 minutes). The mixture was stirred at room temperature for 1 hour, then was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried over magnesium sulfate, filtered through CELITE filter agent, and concentrated under reduced pressure. The crude product was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with ethyl acetate in hexanes) to yield 7.69 g of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow foam.

Part I

A solution of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (7.65 g, 20.8 mmol) in DMF (20 mL) was added dropwise via addition funnel to a solution of *N*-hydroxyphthalimide (4.07 g, 25.0 mmol) and triethylamine (4.3 mL, 31.2 mmol) in DMF (20 mL). The addition funnel was rinsed with DMF (20 mL) and the rinse was added to the reaction solution, which was stirred at room temperature. After 30 minutes, a precipitate formed. The viscous mixture was stirred at room temperature overnight, then diethyl ether (150 mL) was added. The solid was isolated by filtration, washed with diethyl ether, and dried under vacuum to provide 7.44 g of 2-[[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy]-1*H*-isoindole-1,3(2*H*)-dione, which contained some triethylamine hydrochloride. The filtrate was concentrated to yield 8.5 g of a brown oil, which was found to contain product and was combined with the material from above and used in the next step.

Part J

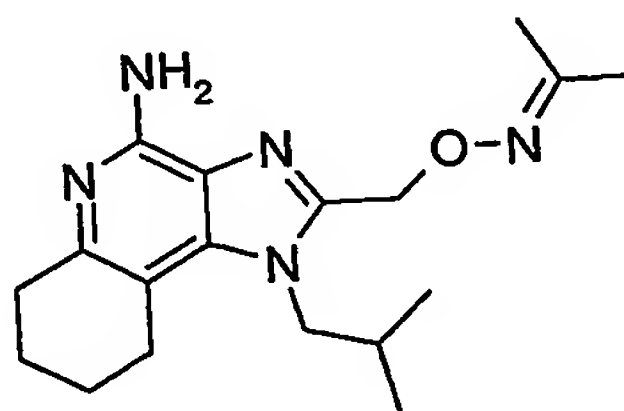
Anhydrous hydrazine (20 mL) was added to a stirred suspension of the material from Part I (approximately 20.8 mmol) in ethanol (150 mL) at room temperature. The mixture became homogeneous after 2 minutes. After 30 minutes, a precipitate had formed. The mixture was stirred for another 1.5 hours, then was filtered through CELITE filter agent. The filtrate was concentrated under reduced pressure to afford crude 2-[(aminooxy)methyl]-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a brown solid, which was used in the next step without purification.

Part K

The material from Part J was dissolved in methanol (150 mL) and acetone (50 mL). The solution was stirred at room temperature for 3 hours, then was concentrated under reduced pressure to yield a brown solid. Dichloromethane (100 mL) was added and the mixture was stirred for 30 minutes, then filtered. The filtrate was concentrated under reduced pressure and purified by chromatography three times on a HORIZON HPFC system (silica gel) to yield 4.11 g of acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime as a pale orange solid.

Example 101

Acetone *O*-{[4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl} oxime



Part A

A mixture of [4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol (15.2 g, 56.2 mmol, U.S. Pat. No. 5,389,640 Example 9), platinum(IV) oxide (7.6 g), and trifluoroacetic acid (75 mL) was hydrogenated at 50 psi (3.5×10^5 Pa) of hydrogen on a Parr apparatus for 2 days. The mixture was diluted with dichloromethane and filtered through CELITE filter agent, which was rinsed afterwards with

dichloromethane and methanol. The filtrate was concentrated under reduced pressure and the residue was partitioned between dichloromethane (250 mL) and 1:1 saturated aqueous sodium bicarbonate/water (250 mL). Some solid formed that was isolated by filtration. The aqueous layer was extracted with dichloromethane (2 x 200 mL). The solid was dissolved in methanol and the resulting solution was combined with the organic layers, concentrated under reduced pressure, and purified by chromatography using a HORIZON HPFC system (silica gel, elution with 10% 1 M NH₃ in methanol/dichloromethane) to afford 4.98 g of [4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as a grey solid.

Part B

Thionyl chloride (2.65 mL, 36.2 mmol) was added dropwise to a stirred suspension of [4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol (4.97 g, 18.1 mmol) in 1,2-dichloroethane (200 mL). The suspension dissolved, then a precipitate formed after 5 minutes. The reaction mixture was stirred at room temperature for 6 hours, then was concentrated under reduced pressure to yield crude 2-(chloromethyl)-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydrochloride, all of which was used in the next step.

Part C

A solution of *N*-hydroxyphthalimide (3.54 g, 21.7 mmol) and triethylamine (7.6 mL, 54.3 mmol) in DMF (25 mL) was added to a suspension of the material from Part B in DMF (25 mL) at room temperature. The reaction mixture was stirred at room temperature overnight, then was concentrated under reduced pressure and used without purification in the next step.

Part D

Hydrazine hydrate (8.8 mL, 181 mmol) was added to a solution of the material from Part C in ethanol (180 mL). The reaction mixture was stirred overnight and a solid formed that was removed by filtration. The filtrate was concentrated under reduced pressure, then was purified by chromatography using a HORIZON HPFC system (silica

gel, gradient elution with 5-10% 1 M NH₃ in methanol/dichloromethane) to afford 4.52 g of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a pale yellow foam.

5 Part E

10 A solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (700 mg, 2.42 mmol) in methanol (12 mL) and acetone (12 mL) was stirred at room temperature for 1 day, then was concentrated under reduced pressure to yield an oil. The oil was diluted with acetonitrile and concentrated under reduced pressure to yield a solid that was recrystallized from acetonitrile. The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to yield 379 mg of acetone *O*-{[4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime as white crystals, mp 176-177 °C.

15 ¹H NMR (300 MHz, DMSO-*d*₆) δ 5.87 (br s, 2H), 5.17 (s, 2H), 4.15 (d, *J* = 7.7 Hz, 2H), 2.91 (m, 2H), 2.67 (m, 2H), 2.03 (m, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.76 (m, 4H), 0.84 (d, *J* = 6.6 Hz, 6H); MS (APCI) *m/z* 330.2 (*M* + *H*)⁺; Anal. calcd for C₁₈H₂₇N₅O: C, 65.62; H, 8.26; N, 21.26. Found: C, 65.53; H, 8.43; N, 21.45.

20 Examples 102-115

20 An aldehyde or ketone from the table below (1.1 equivalents) was added to a test tube containing a solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as described in Parts A-D of Example 101, 29 mg, 0.1 mmol) in methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water

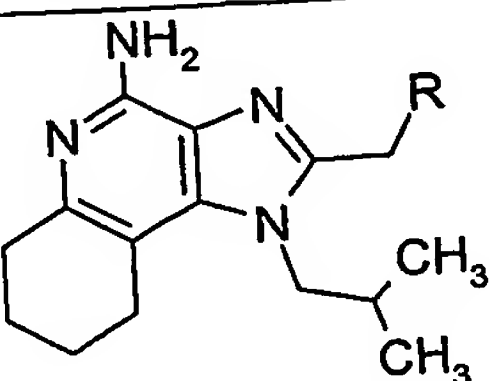
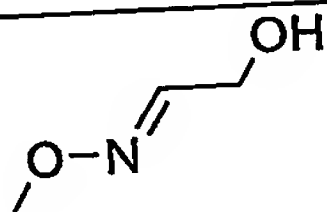
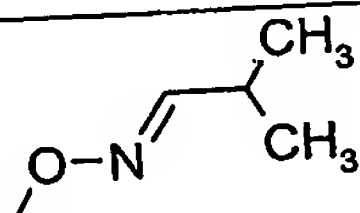
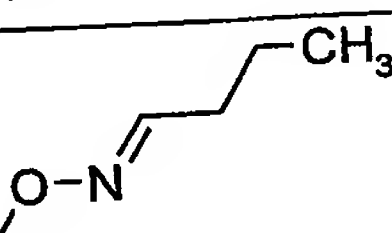
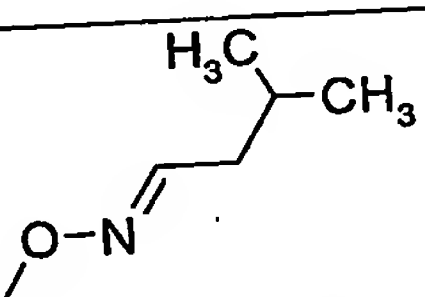
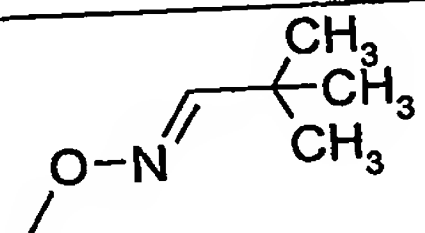
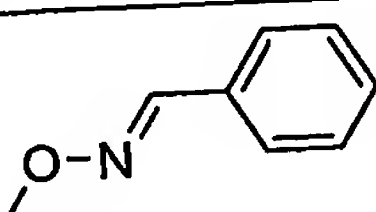
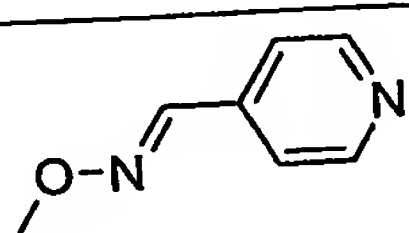
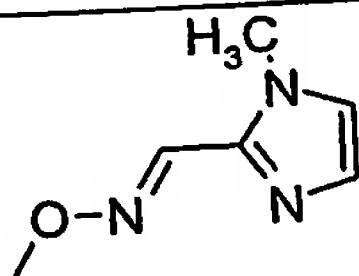
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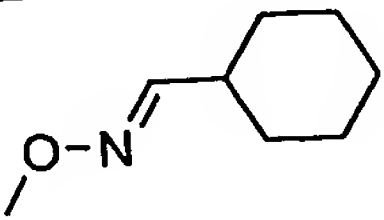
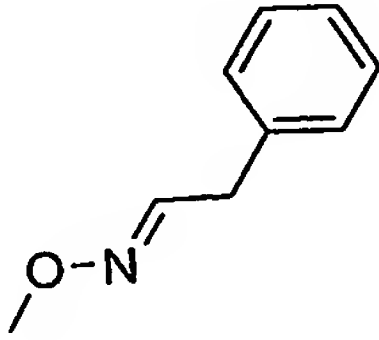
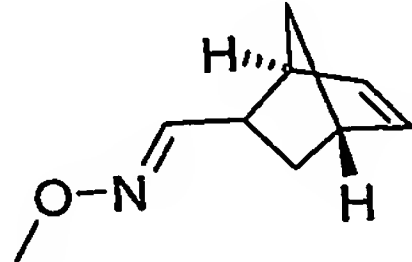
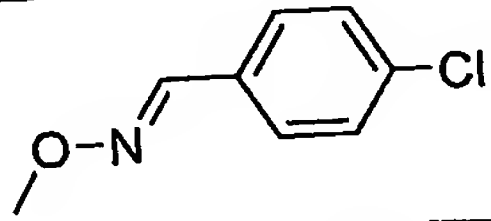
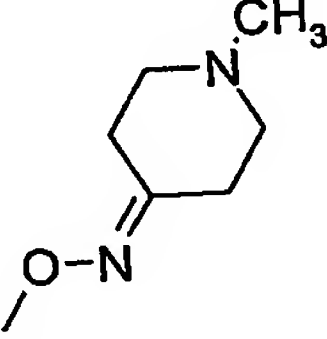
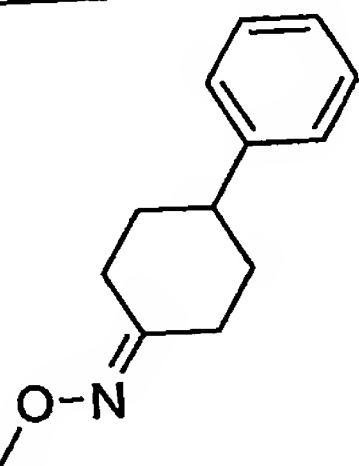
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and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the ketone or aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

5

Examples 102-115

|  | | | |
|--|------------------------------------|---|---------------------|
| Example | Reagent | R | Measured Mass (M+H) |
| 102 | 2-Hydroxyacetaldehyde |  | 332.2056 |
| 103 | Isobutyraldehyde |  | 344.2471 |
| 104 | Butyraldehyde |  | 344.2457 |
| 105 | Isovaleraldehyde |  | 358.2617 |
| 106 | Trimethylacetaldehyde |  | 358.2574 |
| 107 | Benzaldehyde |  | 378.2259 |
| 108 | Isonicotinaldehyde |  | 379.2219 |
| 109 | 1-Methyl-2-imidazolecarboxaldehyde |  | 382.2323 |

| | | | |
|-----|-------------------------------|---|----------|
| 110 | Cyclohexanecarboxaldehyde |  | 384.2725 |
| 111 | Phenylacetaldehyde |  | 392.2444 |
| 112 | 5-Norbornene-2-carboxaldehyde |  | 394.2567 |
| 113 | 4-Chlorobenzaldehyde |  | 412.1871 |
| 114 | 1-Methyl-4-piperidone |  | 385.2735 |
| 115 | 4-Phenylcyclohexanone |  | 446.2913 |

Examples 116-164

An aldehyde or ketone from the table below (1.2 equivalents) was added to a test tube containing a solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-
5 c]quinolin-1-yl}-2-methylpropan-2-ol (prepared as described in Parts A-F of Example 84, 30 mg, 0.1 mmol) in methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified using the method described in Examples 102-115. The table below shows the ketone or aldehyde used for each example,
10 the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Preparation of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-2-carbaldehyde for
Example 116:

5 A solution of *n*-butyllithium in hexanes (2.5 M, 45.5 mL, 1.15 equivalents) was added dropwise to a stirred, -78 °C solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (prepared as described in Example 32 of U.S. Patent 4,689,338, 25.64 g) in tetrahydrofuran (450 mL). The solution was stirred for 10 minutes, then DMF (20.1 mL, 2.3 equivalents) was added. The reaction mixture was allowed to warm to room temperature over 1 hour. The volatiles were removed under reduced pressure and the
10 residue was portioned between ethyl acetate (400 mL) and brine (400 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a brown solid that was purified by flash chromatography (silica gel, gradient elution with 0.5-1% methanol in dichloromethane) to provide 10.5 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-2-carbaldehyde.

15 Preparation of 4-[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]butan-2-one for Example 117:

Part A

20 To a cooled solution of *N*⁴-(2-methylpropyl)quinoline-3,4-diamine (2.15 g, 10 mmol) in DMF (40 mL) was added 3-(2-methyl-1,3-dioxolan-2-yl)propanoic acid (2.40 g, 15 mmol), followed by 4-methylmorpholine (1.6 mL, 15 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (2.9 g, 15 mmol). The resulting suspension was stirred at room temperature and 4-dimethylaminopyridine (0.12 g, 1 mmol) was added. The dark yellow solution was stirred at room temperature for 16
25 hours, then saturated aqueous sodium bicarbonate (100 mL) was added. The mixture was transferred to a separatory funnel and was extracted with dichloromethane (2 x 100 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under
30 reduced pressure to afford an oil that was purified by flash chromatography (silica gel,

elution with 5% methanol in dichloromethane) to provide 2.55 g of *N*-{4-[(2-methylpropyl)amino]quinolin-3-yl}-3-(2-methyl-1,3-dioxolan-2-yl)propanamide.

Part B

5 Water (3 mL) followed by solid sodium hydroxide (0.4 g, 10.7 mmol) were added to a stirred solution of *N*-{4-[(2-methylpropyl)amino]quinolin-3-yl}-3-(2-methyl-1,3-dioxolan-2-yl)propanamide (2.55 g, 7.13 mmol) in ethanol (10 mL). The reaction mixture was heated at reflux for 30 minutes, then was allowed to cool to room temperature and was concentrated under reduced pressure. The resulting aqueous slurry was diluted with water
10 (50 mL) and was extracted with dichloromethane (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 2.3 g of crude 1-(2-methylpropyl)-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline as a clear oil.

15 Part C

mCPBA (60% purity, 2.3 g, 7.95 mmol) was added in portions to a stirred solution of 1-(2-methylpropyl)-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline (2.7 g, 7.95 mmol) in chloroform (40 mL) at room temperature. The reaction mixture was stirred for 20 minutes, then was partitioned between dichloromethane (100
20 mL) and saturated aqueous sodium carbonate (50 mL). The organic layer was washed with saturated aqueous sodium carbonate (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated without purification, concentrated under reduced pressure to yield an orange foam that was used in the next step without purification.

25 Part D

Concentrated ammonium hydroxide (13 mL) followed by *p*-toluenesulfonyl chloride (1.50 g, 7.95 mmol) were added to a rapidly stirred solution of the material from Part C in dichloromethane (40 mL). The *p*-toluenesulfonyl chloride was added in portions. After the mixture was stirred at room temperature for 10 minutes, the mixture was
30 partitioned between chloroform (100 mL) and saturated aqueous sodium carbonate (50 mL). The organic layer was washed with brine (50 mL), dried over sodium sulfate,

filtered, and concentrated under reduced pressure. The crude solid was crystallized from ethyl acetate. A tan solid was isolated by filtration, washed with acetonitrile, and dried at 65 °C under vacuum to provide 1.8 g of 1-(2-methylpropyl)-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

5

Part E

Concentrated hydrochloric acid (0.80 mL, 9.3 mmol) was added to a stirred suspension of 1-(2-methylpropyl)-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.10 g, 3.10 mmol) in water (24 mL). A solution resulted and was stirred at room temperature for 30 minutes. The solution was adjusted to pH 12 with 20% aqueous sodium hydroxide. A white solid precipitated and was isolated by filtration, washed with water, and recrystallized from ethyl acetate to yield 0.6 g of 4-[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]butan-2-one as a monohydrate as a white powder, mp 172-174 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 8.1 Hz, 1H), 6.41 (bs, 2H), 4.34 (d, *J* = 7.5 Hz, 2H), 3.08 (bs, 4H), 2.23 (s, 3H), 2.23-2.15 (m, 1H), 0.95 (d, *J* = 6.9 Hz, 6H); MS (APCI) *m/z* 311 (*M* + *H*)⁺; Anal. Calcd for C₁₈H₂₂N₄O•H₂O: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.03; H, 7.34; N, 17.10.

20

Preparation of 4-{4-amino-1-[5-(methylsulfonyl)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}butan-2-one for Example 118:

Part A

*N*⁴-[5-(methylthio)pentyl]quinoline-3,4-diamine (prepared as described in U.S. Patent 2003/0100764 A1 Example 11 Parts A-D, 4.20 g, 15.3 mmol) was converted into 1.7 g of 2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-[5-(methylthio)pentyl]-1*H*-imidazo[4,5-*c*]quinoline using the method described in Part B of the preparation of 4-[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]butan-2-one (for Example 119) below.

30

Part B

mCPBA (75% purity, 3.23 g, 14.0 mmol) was added in portions to a stirred solution of 2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-[5-(methylthio)pentyl]-1*H*-imidazo[4,5-*c*]quinoline (1.70 g, 4.25 mmol) in chloroform (21 mL) at room temperature. The reaction mixture was stirred for 30 minutes, then concentrated ammonium hydroxide (21 mL) was added followed by portionwise addition of *p*-toluenesulfonyl chloride (0.97 g, 5.1 mmol). After the mixture was stirred at room temperature for 10 minutes, the mixture was partitioned between chloroform (100 mL) and 1% aqueous sodium carbonate (50 mL). The organic layer was washed with 1% aqueous sodium carbonate (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude solid was purified by flash chromatography (silica gel, 5% methanol in dichloromethane) to yield 1.1 g of 2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-[5-(methylthio)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

15 Part C

The general procedure used in Part E of the preparation of 4-(4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl)butan-2-one (for Example 117) above was used to convert 2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-[5-(methylthio)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine into 4-{4-amino-1-[5-(methylthio)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}butan-2-one. The crude solid isolated by filtration was stirred in refluxing ethanol for 1 hour, then the suspension was allowed to cool to room temperature and was stirred for 1 hour. The solid was isolated by filtration, washed with ethanol and dried to afford 4-{4-amino-1-[5-(methylthio)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}butan-2-one in 70% yield as a white powder, mp 179-181 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.02 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 8.1 Hz, 1H), 6.40 (bs, 2H), 4.52 (t, *J* = 7.5 Hz, 2H), 3.13-3.09 (m, 6H), 2.92 (s, 3H), 2.23 (s, 3H), 1.89-1.81 (m, 2H), 1.79-1.67 (m, 2H), 1.60-1.53 (m, 2H); MS (APCI) *m/z* 403 (*M* + *H*)⁺; Anal. Calcd for C₂₀H₂₆N₄O₃S: C, 59.68; H, 6.51; N, 13.92. Found: C, 59.59; H, 6.54; N, 13.82.

Preparation of 4-[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]butan-2-one for Example 119:

Part A

5 *N*-Hydroxysuccinamide (0.80 g, 6.9 mmol) followed by 4-methylmorpholine (0.70 g, 6.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (1.32 g, 6.9 mmol) were added to a 0 °C solution of 3-(2-methyl-1,3-dioxolan-2-yl)propanoic acid (1.00 g, 6.24 mmol) in dichloromethane (12 mL). The solution was allowed to warm to room temperature and was stirred overnight. The reaction mixture was
10 diluted with dichloromethane (10 mL), transferred to a separatory funnel, and washed with water (2 x 10 mL), saturated aqueous sodium bicarbonate (2 x 10 mL), and brine (10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1.1 g of 1-[[3-(2-methyl-1,3-dioxolan-2-yl)propanoyl]oxy]pyrrolidine-2,5-dione as a white solid.

15

Part B

 A suspension of 1-[(3-aminoquinolin-4-yl)amino]-2-methylpropan-2-ol (1.00 g, 4.33 mmol), 1-[[3-(2-methyl-1,3-dioxolan-2-yl)propanoyl]oxy]pyrrolidine-2,5-dione (1.3 g, 5.2 mmol), and pyridine hydrochloride (0.1 g) in toluene (50 mL) was heated at reflux
20 with a Dean Stark trap for 6 hours, then was cooled to room temperature and concentrated under reduced pressure to afford an oil. The oil was dissolved in dichloromethane (100 mL), washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 5% methanol in
25 dichloromethane) to afford 0.6 g of 2-methyl-1-{2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propan-2-ol.

Part C

 mCPBA (75% purity, 0.62 g, 2.7 mmol) was added in portions to a stirred solution
30 of 2-methyl-1-{2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propan-2-ol (0.80 g, 2.25 mmol) in chloroform (12 mL) at room temperature. The

reaction mixture was stirred for 20 minutes, then was partitioned between chloroform (100 mL) and 1% aqueous sodium carbonate (50 mL). The organic layer was washed with 1% aqueous sodium carbonate (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated without purification, concentrated under reduced pressure to yield an orange solid that was used in the next step without purification.

Part D

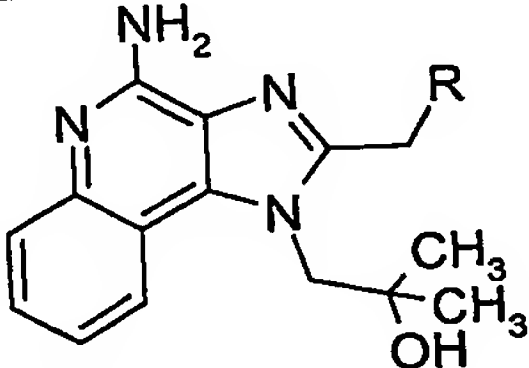
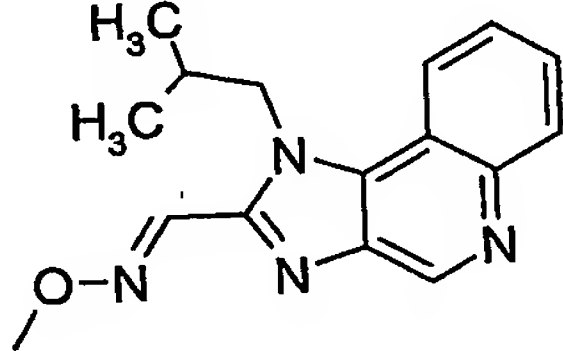
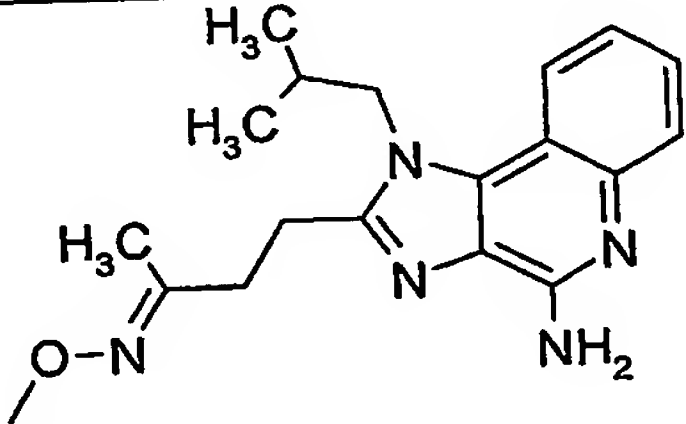
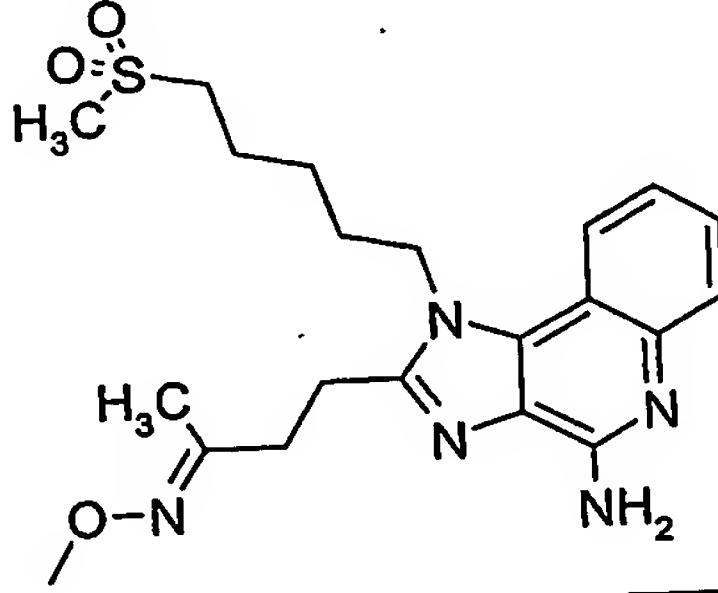
Concentrated ammonium hydroxide (4 mL) followed by *p*-toluenesulfonyl chloride (0.47 g, 2.48 mmol) were added to a rapidly stirred solution of the material from Part C in dichloromethane (12 mL). The *p*-toluenesulfonyl chloride was added in portions. After the mixture was stirred at room temperature for 10 minutes, the mixture was partitioned between chloroform (100 mL) and 1% aqueous sodium carbonate (50 mL). A white solid formed in the aqueous layer that was isolated by filtration, washed with water, and dried to yield 0.2 g of 1-{4-amino-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol. The organic layer was washed with 1% aqueous sodium carbonate (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude solid was stirred in water and sodium carbonate was added to adjust the pH to 10. The mixture was stirred overnight and a solid was isolated by filtration, washed with water, and dried to provide 0.1 g of 1-{4-amino-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol.

Part E

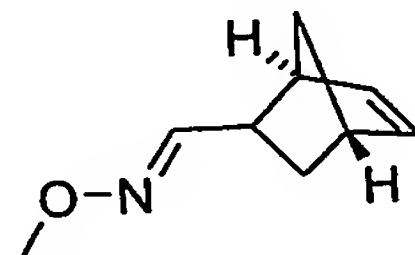
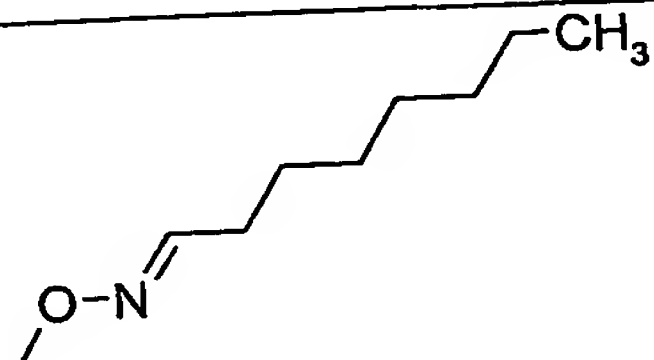
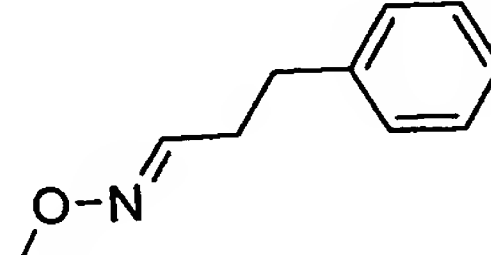
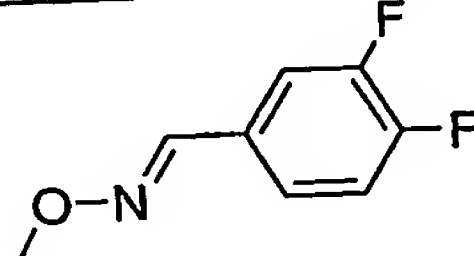
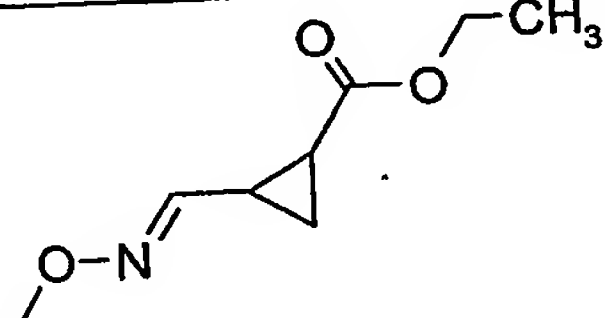
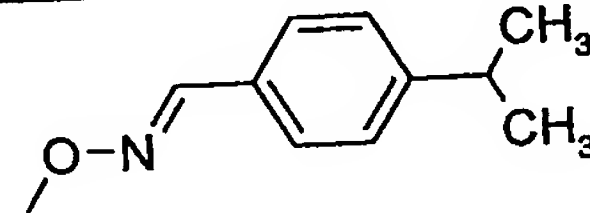
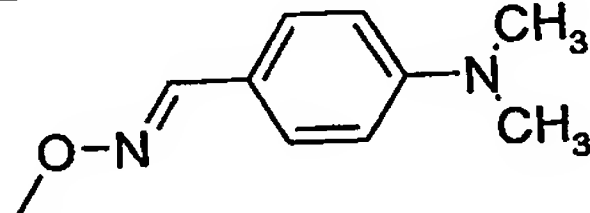
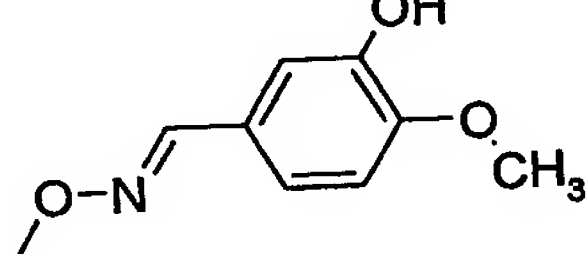
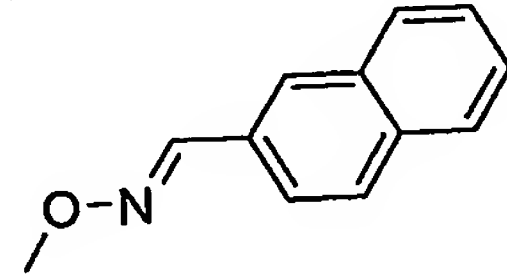
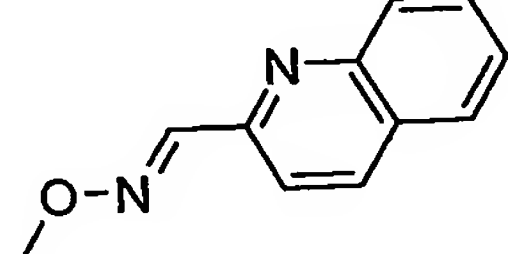
Concentrated hydrochloric acid (0.20 mL, 2.4 mmol) was added to a stirred suspension of 1-{4-amino-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (0.30 g, 0.81 mmol) in water (5 mL). A solution resulted and was stirred at room temperature for 3 hours. The solution was adjusted to pH 13 with 20% aqueous sodium hydroxide. A gummy solid formed. Dichloromethane was added, but the solid did not dissolve. The mixture was poured into a separatory funnel, then the contents of the funnel were filtered. The white solid isolated by filtration was washed with water and dried to yield 0.17 g of 4-[4-amino-1-(2-hydroxy-2-methylpropyl)-

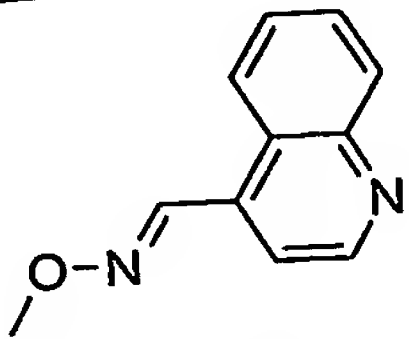
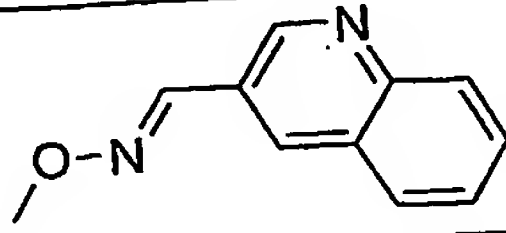
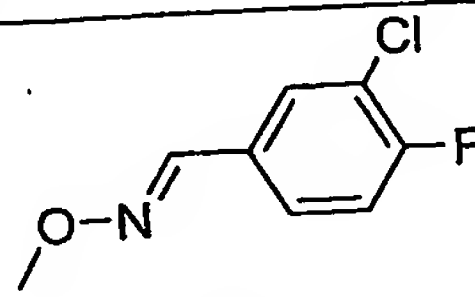
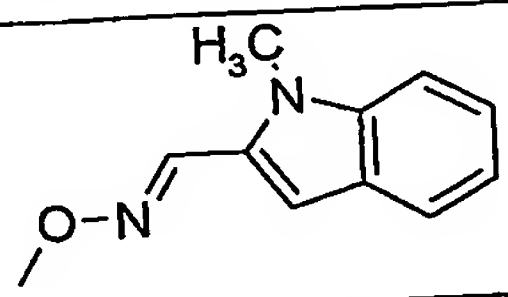
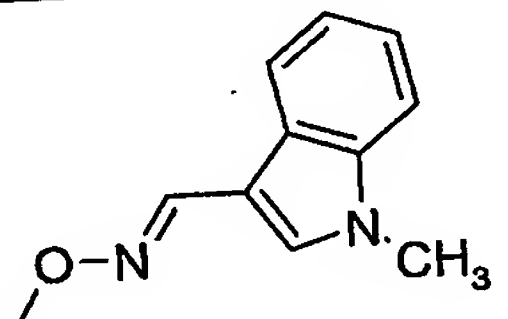
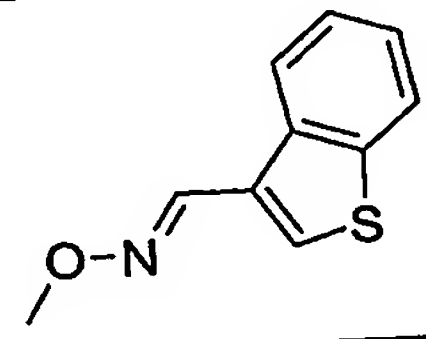
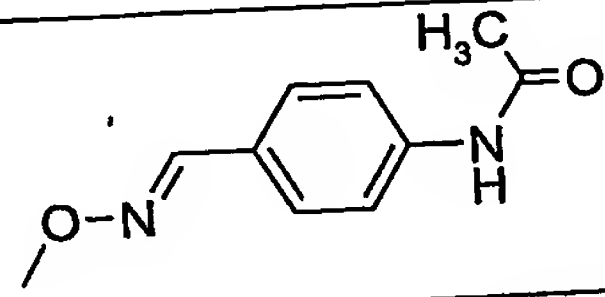
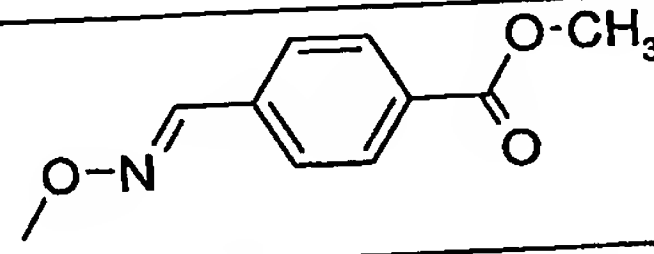
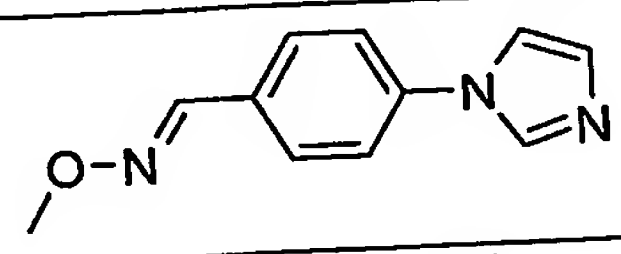
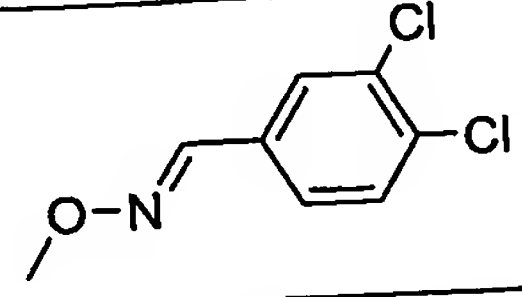
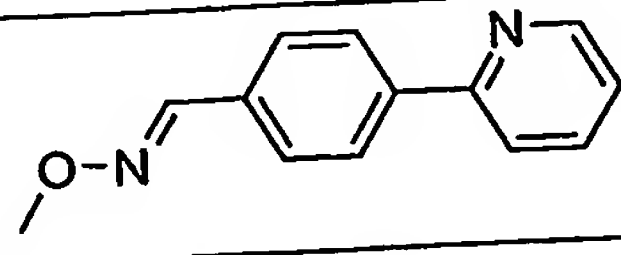
5 1*H*-imidazo[4,5-*c*]quinolin-2-yl]butan-2-one as a white powder, mp 181-184 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.26 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.35 (bs, 2H), 4.79 (s, 1H), 4.57 (bs, 2H), 3.21 (t, *J* = 6.9 Hz, 2H), 3.05 (t, *J* = 6.9 Hz, 2H), 2.20 (s, 3H), 1.18 (bs, 6H); MS (APCI) *m/z* 327 (*M* + *H*)⁺; Anal. Calcd for C₁₈H₂₂N₄O₂: C, 66.24; H, 6.79; N, 17.17. Found: C, 65.85; H, 6.71; N, 17.16.

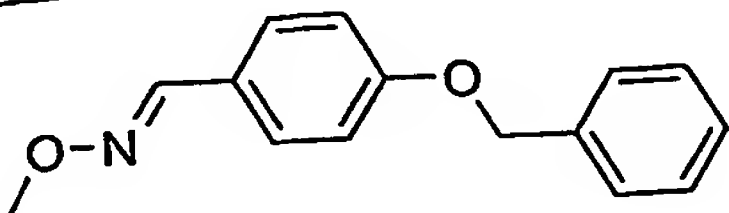
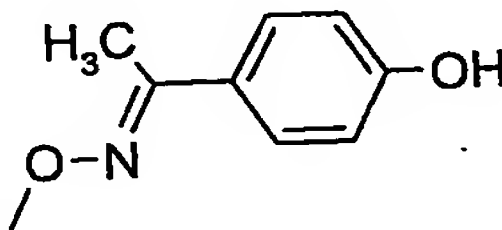
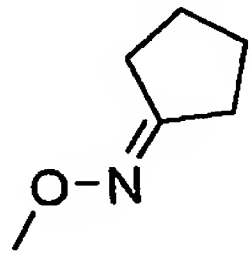
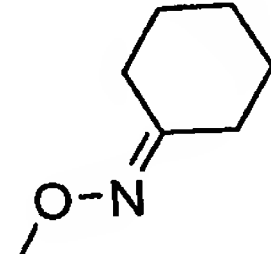
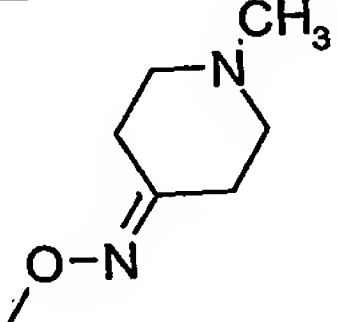
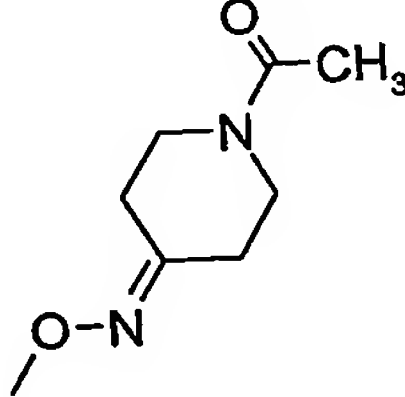
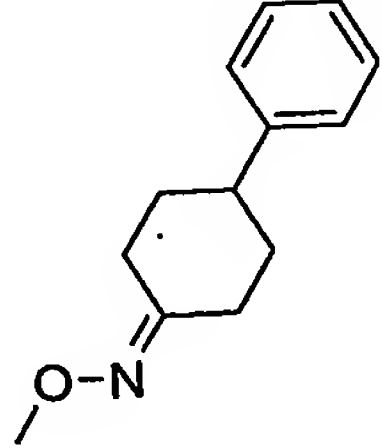
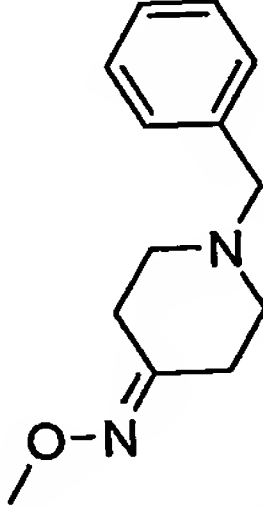
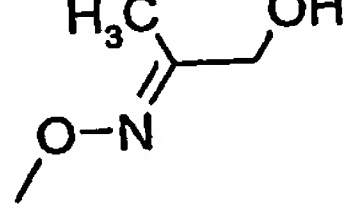
Examples 116-164

|  | | | |
|---|--|---|---------------------------------------|
| Example | Reagent | R | Measured Mass (<i>M</i> + <i>H</i>) |
| 116 | 1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinoline-2-carbaldehyde |  | 537.2717 |
| 117 | 4-[4-Amino-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-2-yl]butan-2-one |  | 594.3264 |
| 118 | 4-{4-Amino-1-[5-(methylsulfonyl)pentyl]-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-2-yl}butan-2-one |  | 686.3196 |

| | | | |
|-----|--|--|----------|
| 119 | 4-[4-Amino-1-(2-hydroxy-2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-2-yl]butan-2-one | | 610.3226 |
| 120 | 2-Hydroxyacetaldehyde | | 344.1735 |
| 121 | Butyraldehyde | | 356.2071 |
| 122 | Isovaleraldehyde | | 370.2233 |
| 123 | 3-Furaldehyde | | 380.1738 |
| 124 | Furfural | | 380.1732 |
| 125 | Tetrahydrofuran-3-carboxaldehyde | | 384.2047 |
| 126 | Benzaldehyde | | 390.1948 |
| 127 | Nicotinaldehyde | | 391.1863 |
| 128 | 2-Thiophenecarboxaldehyde | | 396.1491 |
| 129 | 3-Thiophenecarboxaldehyde | | 396.1526 |
| 130 | 2-Thiazolcarboxaldehyde | | 397.1446 |

| | | | |
|-----|--|---|----------|
| 131 | 5-Norbornene-2-carboxaldehyde |  | 406.2285 |
| 132 | Octanal |  | 412.2706 |
| 133 | 3-Phenylpropionaldehyde |  | 418.2272 |
| 134 | 3,4-Difluorobenzaldehyde |  | 426.1769 |
| 135 | Ethyl 2-formyl-1-cyclopropanecarboxylate |  | 426.2110 |
| 136 | Cuminaldehyde |  | 432.2419 |
| 137 | 4-(Dimethylamino)benzaldehyde |  | 433.2391 |
| 138 | 3-Hydroxy-4-methoxybenzaldehyde |  | 436.1992 |
| 139 | 2-Naphthaldehyde |  | 440.2117 |
| 140 | 2-Quinolinecarboxaldehyde |  | 441.2048 |

| | | | |
|-----|---------------------------------|---|----------|
| 141 | 4-Quinolinecarboxaldehyde |  | 441.2018 |
| 142 | Quinoline-3-carboxaldehyde |  | 441.2027 |
| 143 | 3-Chloro-4-fluorobenzaldehyde |  | 442.1476 |
| 144 | 1-Methylindole-2-carboxaldehyde |  | 443.2213 |
| 145 | 1-Methylindole-3-carboxaldehyde |  | 443.2189 |
| 146 | 1-Benzothiophene-3-carbaldehyde |  | 446.1651 |
| 147 | 4-Acetamidobenzaldehyde |  | 447.2121 |
| 148 | Methyl 4-formylbenzoate |  | 448.2003 |
| 149 | 1-(4-Formylphenyl)-1H-imidazole |  | 456.2140 |
| 150 | 3,4-Dichlorobenzaldehyde |  | 458.1153 |
| 151 | 4-(2-Pyridyl)benzaldehyde |  | 467.2162 |

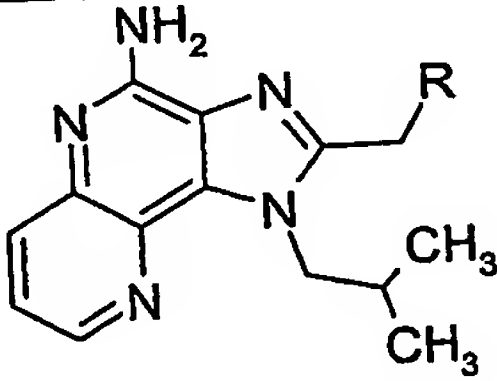
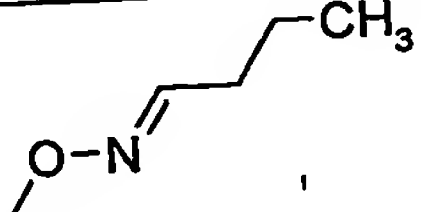
| | | | |
|-----|---------------------------|---|----------|
| 152 | 4-Benzoyloxylbenzaldehyde |  | 496.2368 |
| 153 | 4'-Hydroxyacetophenone |  | 420.2047 |
| 154 | Cyclopentanone |  | 368.2099 |
| 155 | Cyclohexanone |  | 382.2242 |
| 156 | 1-Methyl-4-piperidone |  | 397.2317 |
| 157 | 1-Acetyl-4-piperidone |  | 425.2305 |
| 158 | 4-Phenylcyclohexanone |  | 458.2559 |
| 159 | 1-Benzyl-4-piperidone |  | 473.2637 |
| 160 | Hydroxyacetone |  | 358.1891 |

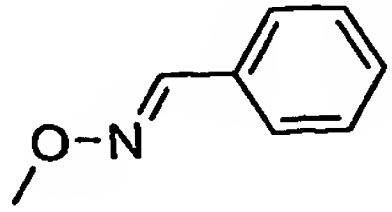
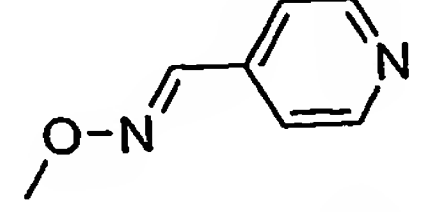
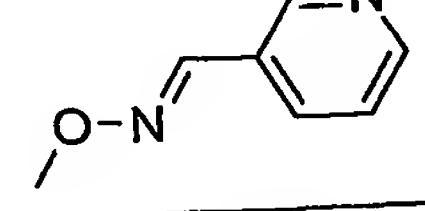
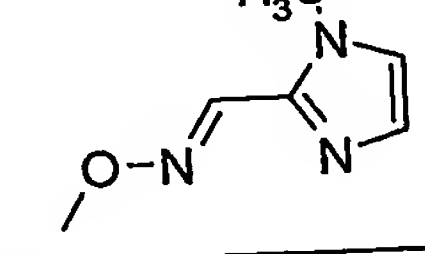
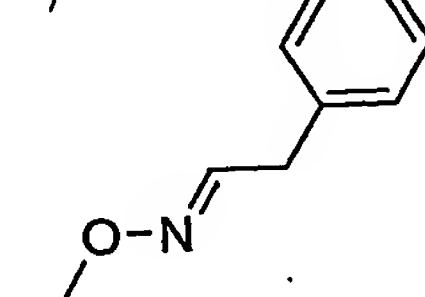
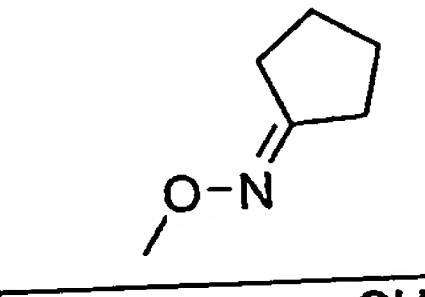
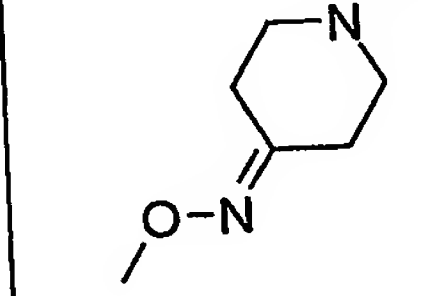
| | | | |
|-----|----------------------|--|----------|
| 161 | 4-Hydroxy-2-butanone | | 372.2002 |
| 162 | Acetoin | | 372.2054 |
| 163 | 3-Acetylpyrrole | | 393.2046 |
| 164 | Diacetone alcohol | | 400.2371 |

Examples 165-172

An aldehyde or ketone from the table below (1.1 equivalents) was added to a test tube containing a solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-1*H*-imidazo[4,5-
 5 *c*][1,5]naphthyridin-4-amine (prepared as described in Parts A-H of Example 95, 29 mg, 0.1 mmol) in methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature for 3 hours. The solvent was removed by vacuum centrifugation. The compounds were purified using the method described in Examples 102-115. The table below shows the ketone or aldehyde used for each example, the structure of the
 10 resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 165-172

|  | | | |
|---|---------------|---|---------------------|
| Example | Reagent | R | Measured Mass (M+H) |
| 165 | Butyraldehyde |  | 341.2074 |

| | | | |
|-----|------------------------------------|---|----------|
| 166 | Benzaldehyde |  | 375.1906 |
| 167 | Isonicotinaldehyde |  | 376.1861 |
| 168 | Nicotinaldehyde |  | 376.1857 |
| 169 | 1-Methyl-2-imidazolecarboxaldehyde |  | 379.2014 |
| 170 | Phenylacetaldehyde |  | 389.2124 |
| 171 | Cyclopentanone |  | 353.2108 |
| 172 | 1-Methyl-4-piperidone |  | 382.2366 |

Examples 173-192

3-Bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine was prepared according to the published procedure (Zhang, N. et al, *J. Med. Chem.*, 45, 2832-2840 (2002)). Under a nitrogen atmosphere, a solution of 3-bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine (28.70 g, 94.94 mmol) and triisopropyl borate (26.3 mL, 114 mmol) in dry THF was cooled to -70 °C. *n*-Butyllithium (45.6 mL, 114 mmol) was added dropwise over a period of 1.5 hours. The reaction was stirred for an additional 30 minutes and then allowed to warm to -20 °C. Dilute aqueous ammonium chloride was added, and the mixture was allowed to warm to ambient temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic fractions were concentrated under reduced pressure, and methanol was added to the

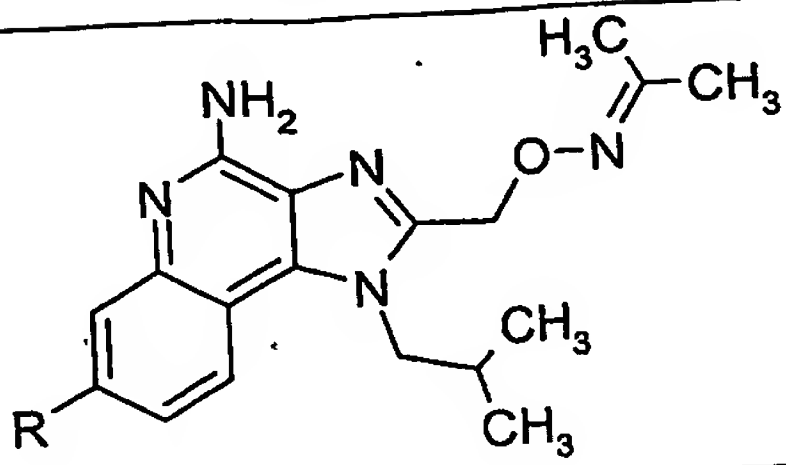
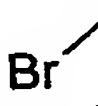
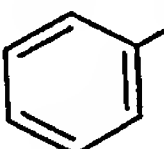
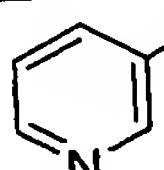
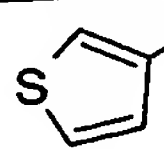
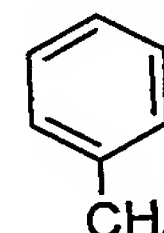
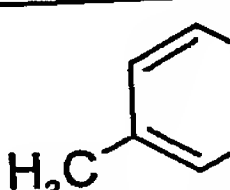
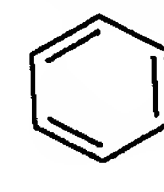
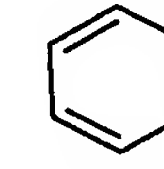
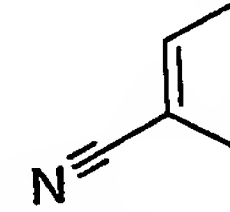
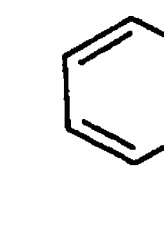

resulting oil. A solid formed, which was stirred with water for two days, isolated by filtration, and dried under reduced pressure to provide 18.19 g of 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid as a white solid.

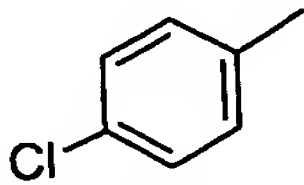
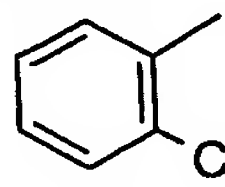
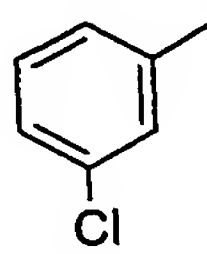
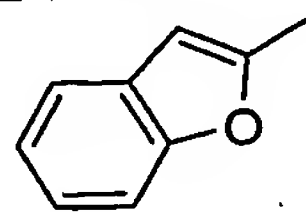
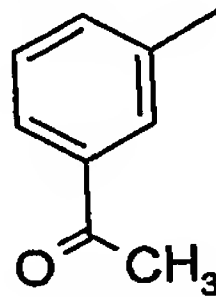
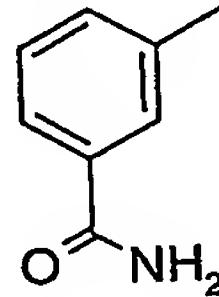
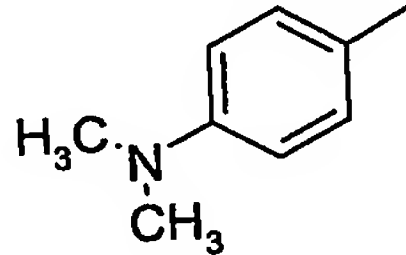
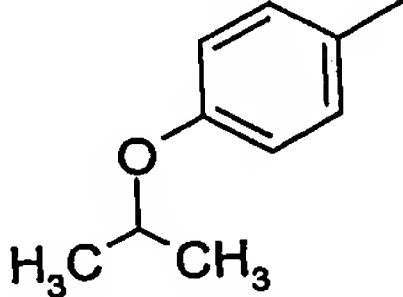
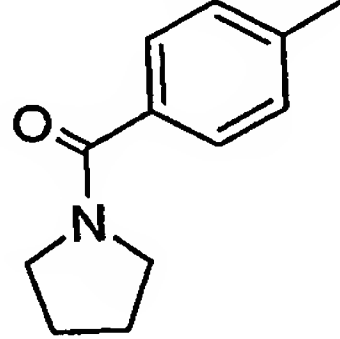
The compounds in the table below were prepared according to the following method. A solution of 2-[(aminooxy)methyl]-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as described in Parts A-J of Example 100, 80 mg, 0.20 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.22 mmol) indicated in the table below and *n*-propanol (3.2 mL) were sequentially added, and the test tube was purged with nitrogen. The reaction mixture was sonicated until a solution formed. Palladium (II) acetate (0.292 mL of a 0.018 M solution in toluene, 0.0053 mmol), 2M aqueous sodium carbonate solution (1.2 mL), deionized water (225 μ L), and a solution of 0.15 M triphenylphosphine in *n*-propanol (106 μ L, 0.0159 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated to 80 °C overnight in a sand bath. For Example 183, the solvent was removed by vacuum centrifugation, and glacial acetic acid (1 mL), tetrahydrofuran (1 mL), and deionized water (1 mL) were added to the test tube. The reaction was heated overnight at 60 °C. The solvent was removed from the test tubes by vacuum centrifugation.

The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the following procedure. Hydrochloric acid (3 mL of 1 N) was added to adjust each example to pH 5-7, and the resulting solution was passed through the cartridge optionally using light nitrogen pressure. The cartridge was washed with methanol (5 mL) optionally using light nitrogen pressure and transferred to a clean test tube. A solution of 1% ammonia in methanol (2 x 5 mL) was then passed through the cartridge optionally using light nitrogen pressure, and the basic solution was collected and concentrated.

The compounds were purified as described in Examples 102-115. The table below shows the boronic acid used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

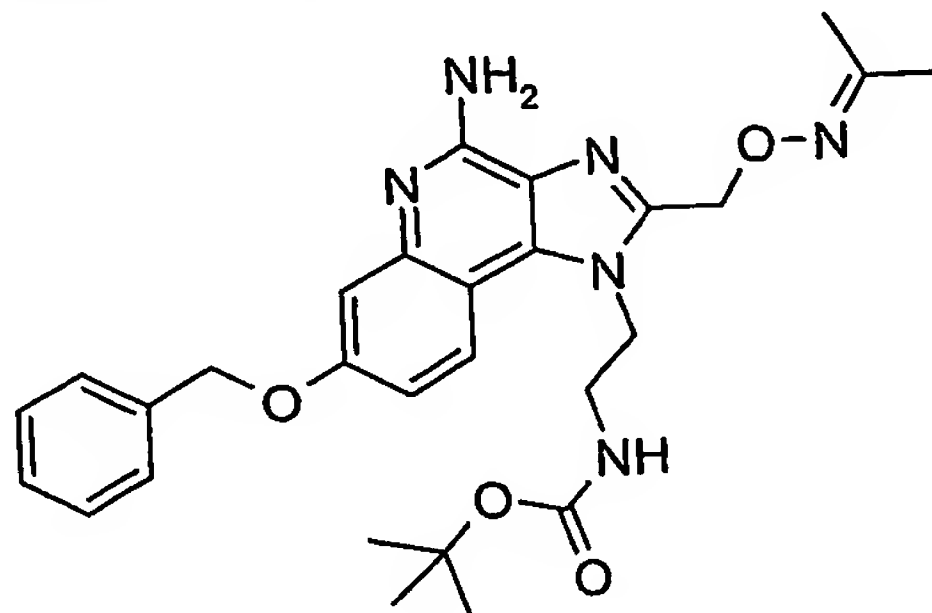
Examples 173-192

|  | | | |
|--|--|---|---------------------|
| Example | Reagent | R | Measured Mass (M+H) |
| 173 | None |  | 404.1086 |
| 174 | Phenylboronic acid |  | 402.2313 |
| 175 | Pyridine-3-boronic acid |  | 403.2241 |
| 176 | Thiophene-3-boronic acid |  | 408.1819 |
| 177 | 3-Methylphenylboronic acid |  | 416.2418 |
| 178 | 4-Methylphenylboronic acid |  | 416.2426 |
| 179 | <i>o</i> -Tolylboronic acid |  | 416.2428 |
| 180 | (2-Hydroxyphenyl)boronic acid |  | 418.2227 |
| 181 | 4-Cyanophenylboronic acid |  | 427.2238 |
| 182 | (2-Hydroxymethylphenyl)boronic acid dehydrate |  | 432.2367 |
| 183 | 5-(<i>tert</i> -Butyldimethylsilanyloxymethyl)pyridine-3-boronic acid |  | 433.2316 |

| | | | |
|-----|--|---|----------|
| 184 | 4-Chlorophenylboronic acid |  | 436.1860 |
| 185 | 2-Chlorophenylboronic acid |  | 436.1909 |
| 186 | 3-Chlorophenylboronic acid |  | 436.1902 |
| 187 | Benzo[B]furan-2-boronic acid |  | 442.2219 |
| 188 | 3-Acetylphenylboronic acid |  | 444.2365 |
| 189 | (3-Aminocarbonylphenyl)boronic acid |  | 445.2321 |
| 190 | 4-(<i>N,N</i> -Dimethylamino)phenylboronic acid |  | 445.2697 |
| 191 | 4-Isopropoxyphenylboronic acid |  | 460.2668 |
| 192 | 4-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 499.2792 |

Example 193

tert-Butyl 2-[4-amino-7-(benzyloxy)-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate



5 Part A

A mixture of triethyl orthoformate (92 mL, 0.55 mol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55 °C for 90 minutes and then cooled to 45 °C. A solution of 3-benzyloxyaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period 45 minutes while maintaining the reaction temperature below 50 °C. The reaction was then heated at 45 °C for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was cooled to 1 °C, and the product was isolated by filtration and washed with cold ethanol (~400 mL) until the filtrate was colorless. 5-{{(3-benzyloxy)phenylimino}methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid.

¹H NMR (300MHz, DMSO-*d*₆) : δ 11.21 (d, *J* = 14.2 Hz, 1H), 8.61 (d, *J* = 14.2 Hz, 1H), 7.49-7.30 (m, 7H), 7.12 (dd, *J* = 8.1, 1.96 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.16 (s, 2H), 1.68 (s, 6H).

20 Part B

A mixture of 5-{{(3-benzyloxy)phenylimino}methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A heat transfer fluid (800 mL) was heated to 100 °C and then slowly added to a flask containing DOWTHERM A heat transfer fluid (1.3 L, heated at 210 °C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to fall below 207 °C. Following the addition, the reaction was stirred at 210 °C for one hour, and then allowed to cool to ambient

temperature. A precipitate formed, which was isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 L), and dried in an oven to provide 76.5 g of 7-benzyloxyquinolin-4-ol as a tan powder.

¹H NMR (300MHz, DMSO-*d*₆) : δ 11.53 (s, 1H), 7.99 (dd, *J* = 2.4, 7.4Hz, 1H), 7.79 (d, *J* = 7.4Hz, 1H), 7.50-7.32 (m, 5H), 7.00 (s, 1H), 6.98 (dd, *J* = 2.5, 7.4Hz, 1H), 5.93 (d, *J* = 7.5Hz, 1H), 5.20 (s, 2H).

Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125 °C with vigorous stirring. Nitric acid (23.11 mL of 16 M) was slowly added over a period of 30 minutes while maintaining the reaction temperature between 121 °C and 125 °C. After the addition, the reaction was stirred at 125 °C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder.

¹H NMR (300MHz, DMSO-*d*₆) : δ 12.77 (s, 1H), 9.12 (s, 1H), 8.17 (dd, *J* = 3.3, 6.3Hz, 1H), 7.51-7.33 (m, 5H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).

Part D

DMF (100 mL) was cooled to 0 °C, and phosphorous oxychloride (27.5 mL, 0.295 mol) was added dropwise. The resulting solution was stirred for 25 minutes and then added dropwise to a mixture of 7-benzyloxy-3-nitroquinolin-4-ol (72.87 g, 0.2459 mol) in DMF (400 mL). Following the addition, the reaction was heated at 100 °C for 5 minutes, cooled to ambient temperature, and poured into ice water with stirring. A tan precipitate formed, which was isolated by filtration and dissolved in dichloromethane. The resulting solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 72.9 g of 7-benzyloxy-4-chloro-3-nitroquinoline as a light brown solid.

¹H NMR (300MHz, DMSO-*d*₆) : δ 9.34 (s, 1H), 8.36 (d, *J* = 8.7Hz, 1H), 7.71 (d, *J* = 2.4Hz, 1H), 7.66 (dd, *J* = 2.4, 9.3Hz, 1H), 7.56-7.51 (m, 2H), 7.46-7.34 (m, 3H), 5.40 (s, 2H).

Part E

tert-Butyl 2-aminoethylcarbamate (54.1 g, 338 mmol) was added to a stirred solution of 7-benzyloxy-4-chloro-3-nitroquinoline (88.6 g, 282 mmol) and triethylamine (58.9 mL, 422 mmol) in DMF (800 mL) at room temperature. The reaction mixture was stirred for 4 hours, then was poured onto stirred hot water in a beaker to precipitate a yellow solid that was isolated by filtration and dried under vacuum at 65 °C to yield 123.7 g of *tert*-butyl 2-[[7-(benzyloxy)-3-nitroquinolin-4-yl]amino]ethylcarbamate.

Part F

A mixture of *tert*-butyl 2-[[7-(benzyloxy)-3-nitroquinolin-4-yl]amino]ethylcarbamate (10.0 g, 22.8 mmol), 5% platinum on carbon (1 g), and ethyl acetate (100 mL) was hydrogenated on a Parr apparatus at 30 psi (2.1×10^5 Pa) of hydrogen overnight. The reaction mixture was filtered through CELITE filter agent, which was rinsed afterwards with methanol. The filtrate was concentrated under reduced pressure and used directly in the next step.

Part G

Chloroacetyl chloride (2.00 mL, 25.1 mmol) was added to a solution of the material from Part F and triethylamine (6.40 mL, 45.6 mmol) in dichloromethane (200 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes, then was concentrated under reduced pressure. The residue was dissolved in ethanol (200 mL) and the solution was stirred at room temperature for 4 days. The solution was concentrated to yield a brown foam that was purified by chromatography using a HORIZON HPFC system (silica gel, elution with 5% methanol/dichloromethane) to provide 4.87 g of *tert*-butyl 2-[7-(benzyloxy)-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate as a yellow foam.

Part H

*m*CPBA (77% purity, 5.84 g, 26.1 mmol) was added to a stirred solution of *tert*-butyl 2-[7-(benzyloxy)-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (4.87 g, 10.4 mmol) in chloroform (100 mL) at room temperature. After 30 minutes, the

reaction mixture was transferred to a separatory funnel and washed with 1% aqueous sodium carbonate (100 mL). The organic layer was dried over magnesium sulfate and filtered. The filtrate was used in the next step.

5 Part I

Concentrated ammonium hydroxide (50 mL) was added to the solution from Part H at room temperature. The mixture was stirred for 2 minutes, and then *p*-toluenesulfonyl chloride (2.39 g, 12.5 mmol) was added. The reaction mixture was stirred for 30 minutes then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The organic layers were combined, 10 dried over magnesium sulfate, filtered, and concentrated to yield a brown foam. The foam was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-10% methanol/dichloromethane) to yield 2.71 g of *tert*-butyl 2-[4-amino-7-(benzyloxy)-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate as a yellow 15 foam.

Part J

A solution of *tert*-butyl 2-[4-amino-7-(benzyloxy)-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (2.70 g, 5.60 mmol) in DMF (10 mL) was 20 added to a stirred solution of *N*-hydroxyphthalimide (1.10 g, 6.72 mmol) and triethylamine (1.56 mL, 11.2 mmol) in DMF (10 mL) at room temperature. A solid formed after 10 minutes. After 1.5 hours, dichloromethane (50 mL) was added and the solid was isolated by filtration, washed with dichloromethane followed by diethyl ether, and dried under vacuum to yield 3.15 g of *tert*-butyl 2-(4-amino-7-(benzyloxy)-2-[[1,3-dioxo-1,3-dihydro-25 2*H*-isoindol-2-yl)oxy]methyl}-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate as an off-white solid.

Part K

Hydrazine hydrate (0.753 mL, 15.5 mmol) was added to a stirred suspension of 30 *tert*-butyl 2-(4-amino-7-(benzyloxy)-2-[[1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (3.15 g, 5.18 mmol) in

ethanol (50 mL). The suspension was stirred at room temperature for 3 hours, then was filtered. The filtrate was concentrated under reduced pressure to yield 2.43 g of crude *tert*-butyl 2-[4-amino-2-[(aminooxy)methyl]-7-(benzyloxy)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate that was used without purification in the next step.

5

Part L

A solution of the material from Part K in acetone (25 mL) and methanol (25 mL) was stirred at room temperature overnight, then was concentrated under reduced pressure to yield a yellow solid that was purified by chromatography using a HORIZON HPFC system (silica gel, elution with 10% methanol/dichloromethane) to afford 2.27 g of *tert*-butyl 2-[4-amino-7-(benzyloxy)-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate as a foam.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.09 (d, *J* = 9.2 Hz, 1H), 7.29-7.52 (m, 5H), 7.16 (m, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 6.94 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.58 (br s, 2H), 5.24 (s, 2H), 5.22 (s, 2H), 4.63 (m, 2H), 3.39 (m, 2H), 1.82 (s, 3H), 1.79 (s, 3H), 1.36 (s, 9H); MS (APCI) *m/z* 519.2 (*M* + *H*)⁺.

10

15

Examples 194-217

To a stirred solution of *tert*-butyl 2-[4-amino-7-(benzyloxy)-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (prepared as described in Example 193, 2.26 g, 4.36 mmol) in dichloromethane (40 mL) was added 4 M HCl in dioxane (10 mL), causing a precipitate to form immediately. Over several hours, methanol (80 mL) and additional 4 M HCl in dioxane (10 mL) were added. The mixture was concentrated under reduced pressure, then was diluted with dichloromethane (50 mL) and trifluoroacetic acid (10 mL). The cloudy suspension was stirred at room temperature for 3.5 hours, then was concentrated under reduced pressure to yield a paste. The paste was concentrated from dichloromethane and diethyl ether to yield 3.02 g of acetone *O*-{[4-amino-1-(2-aminoethyl)-7-(benzyloxy)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime tris(trifluoroacetate) as a yellow solid.

20

25

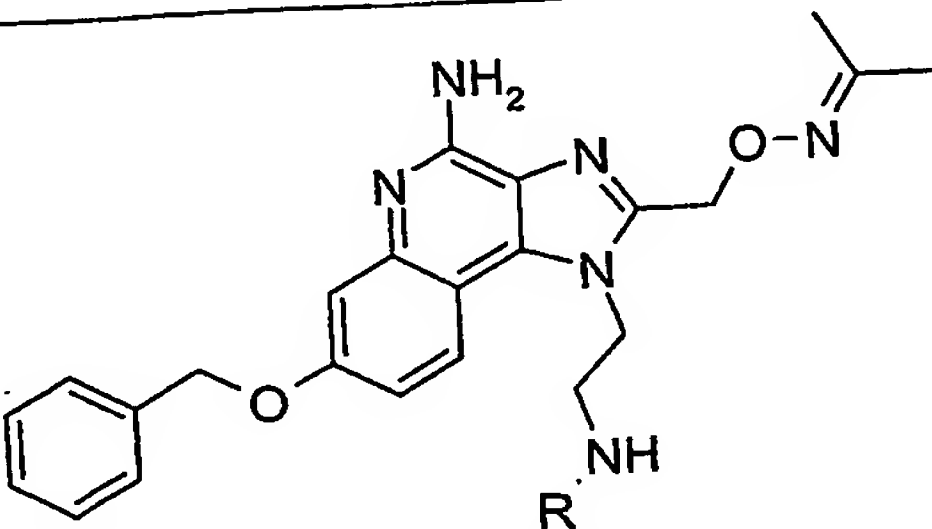
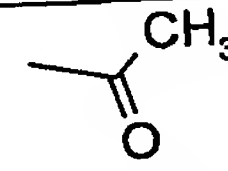
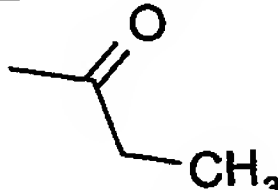
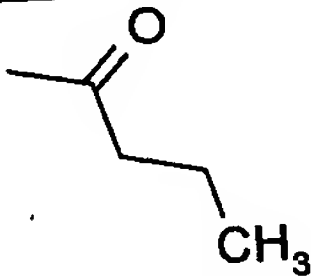
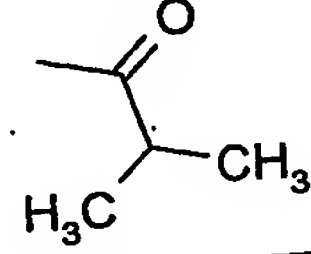
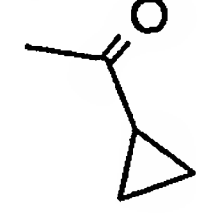
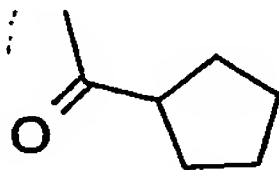
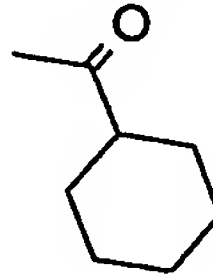
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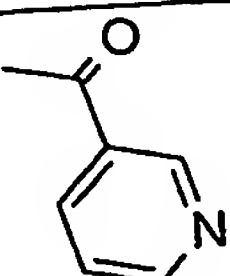
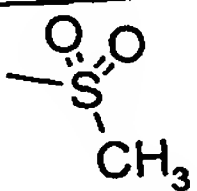
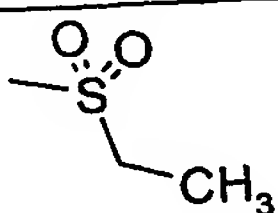
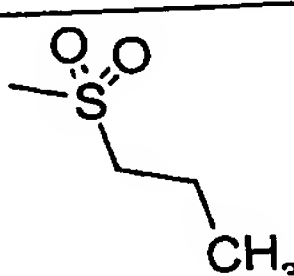
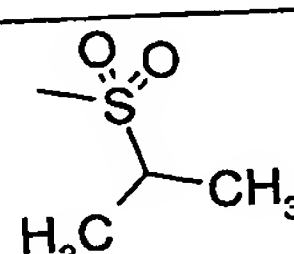
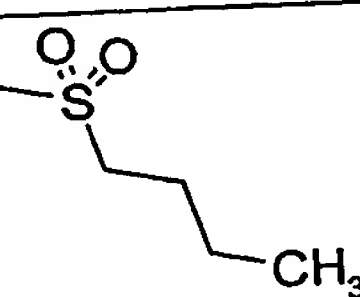
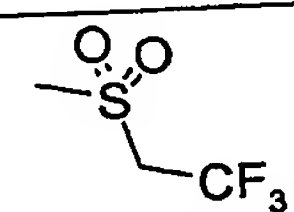
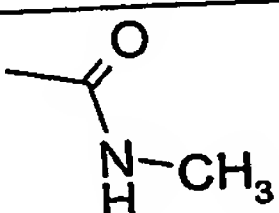
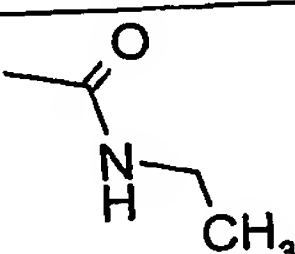
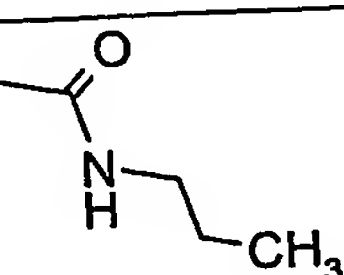
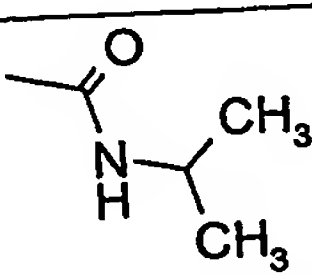
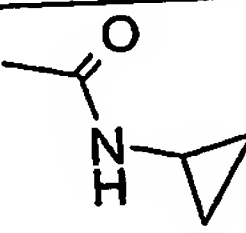
A reagent from the table below (1.1 equivalents, 0.11 mmol) can be added to a test tube containing a solution of acetone *O*-{[4-amino-1-(2-aminoethyl)-7-(benzyloxy)-1*H*-

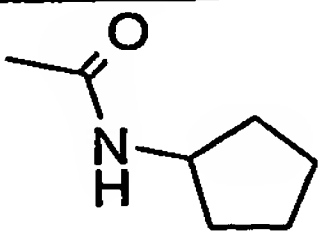
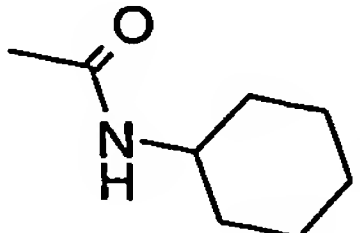
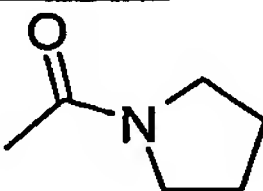
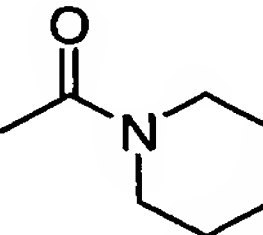
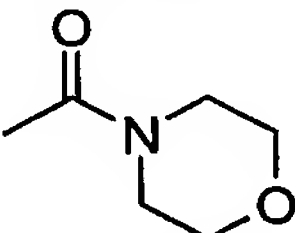
imidazo[4,5-c]quinolin-2-yl)methyl} oxime tris(trifluoroacetate) (76 mg, 0.10 mmol) and triethylamine (73 μ L, 0.50 mmol) in chloroform (1 mL), and the reaction and purification can be carried out according to the procedure described in Examples 60-83. The table below shows a reagent that can be used for each example and the structure of the resulting compound.

5

Examples 194-217

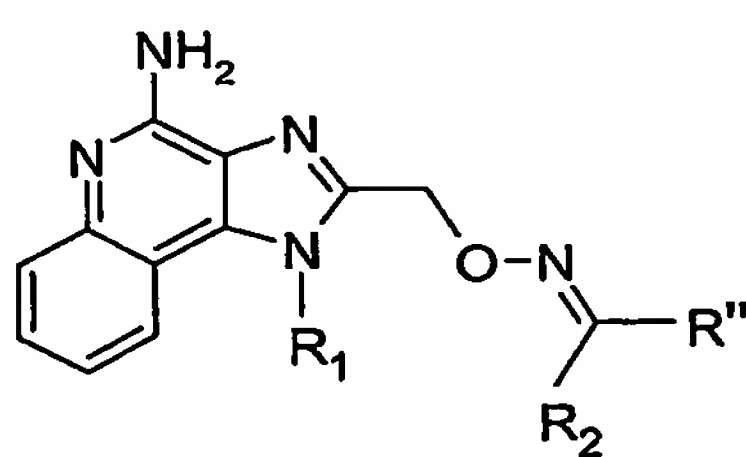
|  | | |
|---|-------------------------------|---|
| Example | Reagent | R |
| 194 | Acetyl chloride |  |
| 195 | Propionyl chloride |  |
| 196 | Butyryl chloride |  |
| 197 | Isobutyryl chloride |  |
| 198 | Cyclopropanecarbonyl chloride |  |
| 199 | Cyclopentanecarbonyl chloride |  |
| 200 | Cyclohexanecarbonyl chloride |  |

| | | |
|-----|---|---|
| 201 | Nicotinoyl chloride hydrochloride |  |
| 202 | Methanesulfonyl chloride |  |
| 203 | Ethanesulfonyl chloride |  |
| 204 | Propanesulfonyl chloride |  |
| 205 | Isopropylsulfonyl chloride |  |
| 206 | Butanesulfonyl chloride |  |
| 207 | 2,2,2-Trifluoroethanesulfonyl chloride |  |
| 208 | Methyl isocyanate |  |
| 209 | Ethyl isocyanate |  |
| 210 | Propyl isocyanate |  |
| 211 | Isopropyl isocyanate |  |
| 212 | Cyclopropyl isocyanate |  |

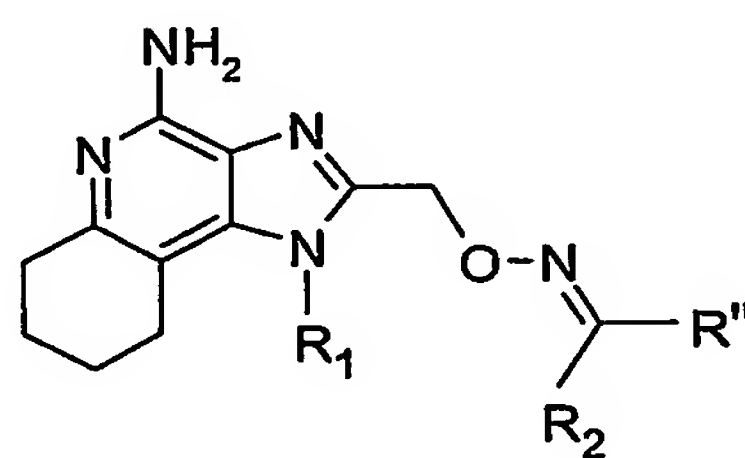
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|-----|--------------------------------|--|
| 213 | Cyclopentyl isocyanate |  |
| 214 | Cyclohexyl isocyanate |  |
| 215 | 1-Pyrrolidinecarbonyl chloride |  |
| 216 | 1-Piperidinecarbonyl chloride |  |
| 217 | 4-Morpholinecarbonyl chloride |  |

Exemplary Compounds

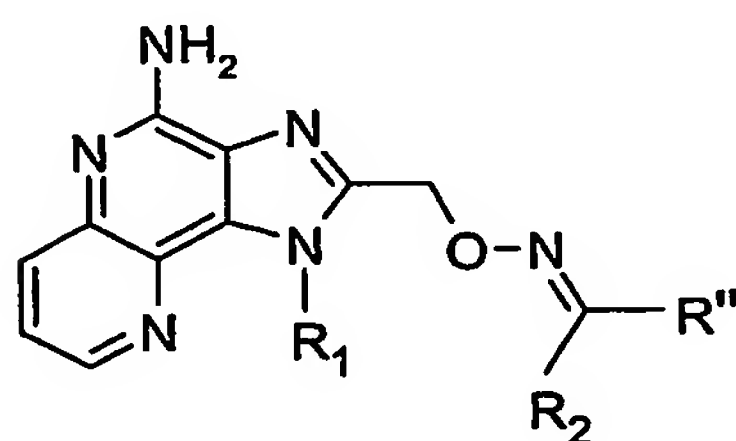
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIe, IVc, Va, and VIa) and the following R¹, R₂, and R₁ substituents, wherein each line of the table is matched with Formula IIIe, IVc, Va, or VIa to represent a specific embodiment of the invention.



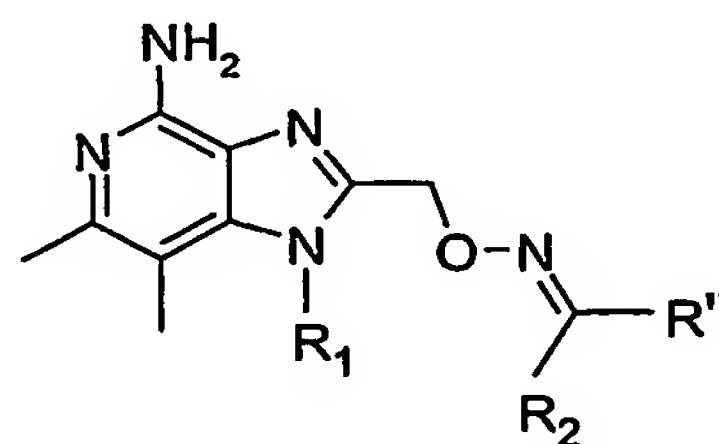
IIIe



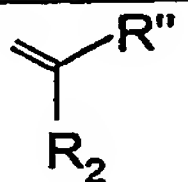
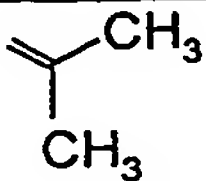
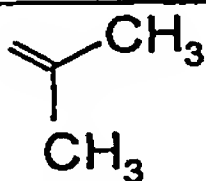
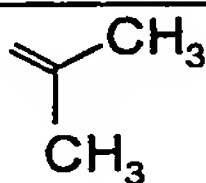
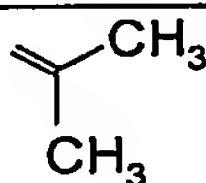
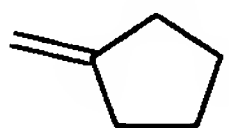
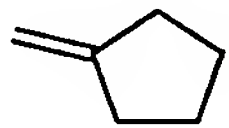
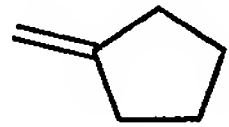
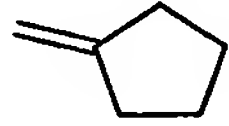
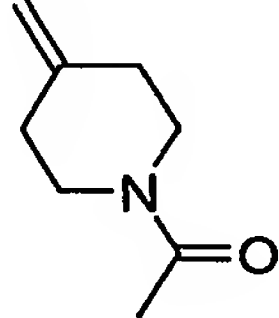
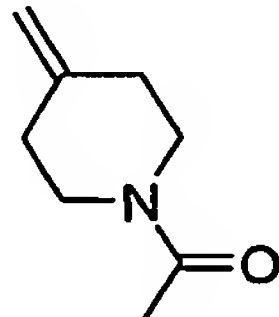
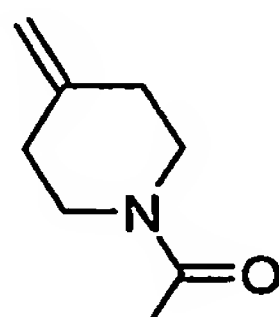
IVc

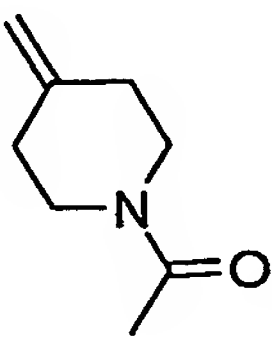


Va



VIa

| | |
|---|--|
|  | R ₁ |
|  | 2-methylpropyl |
|  | 2-hydroxy-2-methylpropyl |
|  | 2-methyl-2-[(methylsulfonyl)amino]propyl |
|  | 4-[(methylsulfonyl)amino]butyl |
|  | 2-methylpropyl |
|  | 2-hydroxy-2-methylpropyl |
|  | 2-methyl-2-[(methylsulfonyl)amino]propyl |
|  | 4-[(methylsulfonyl)amino]butyl |
|  | 2-methylpropyl |
|  | 2-hydroxy-2-methylpropyl |
|  | 2-methyl-2-[(methylsulfonyl)amino]propyl |

| | |
|---|--------------------------------|
|  | 4-[(methylsulfonyl)amino]butyl |
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CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to induce cytokine biosynthesis
5 when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity
is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN- α and
TNF- α , respectively) secreted into culture media as described by Testerman et. al. in
“Cytokine Induction by the Immunomodulators Imiquimod and S-27609”, *Journal of*
10 *Leukocyte Biology*, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA
vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole
15 blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1
with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution
(HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and
resuspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48
well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson
20 Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media
containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO
25 concentration should not exceed a final concentration of 1% for addition to the culture
wells. The compounds are generally tested at concentrations ranging from 30-0.014 μ M.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF- α) when tested using the method described below.

TNF- α INHIBITION IN MOUSE CELLS

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor- α (TNF- α) production upon stimulation by lipopolysaccharide (LPS).

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Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3×10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS).

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Cell suspension (100 μ L) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3×10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

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Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5 μ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC₇₀ concentration as measured by a dose response assay.

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Incubation

A solution of test compound (1 μ L) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μ L, EC₇₀ concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

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TNF- α Analysis

Following the incubation the supernatant is removed with a pipet. TNF- α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource

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International, Camarillo, CA). Results are expressed in pg/mL. TNF- α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

5 Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4×10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μ L) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1×10^5 cells/well. The plates are incubated for 3 hours.

10 Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

15 The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC₇₀ concentration as measured by dose response assay.

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Incubation

A solution of test compound (200 μ l) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μ L, EC₇₀ concentration \sim 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF- α Analysis

Following the incubation the supernatant is removed with a pipet. TNF- α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF- α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.